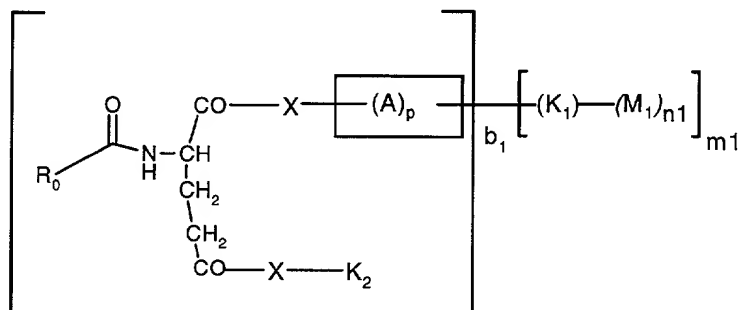


CLAIMS:

1. A diagnostic, therapeutic or radiotherapeutic or chemotherapeutic composition for visualization, therapy, chemotherapy or radiotherapy of tissues or organs that overexpress folate-binding protein comprising:

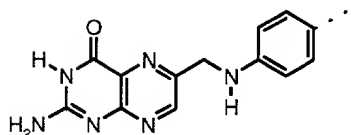
- a) a folate-receptor binding ligand comprising one or more folate-receptor binding residues, at least one of which is conjugated through its alpha carboxylate via an optional linking group to one or more macrocyclic or non-macrocyclic metal-chelating ligand radicals that are optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive metals capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic, chemotherapeutic, or radiotherapeutic effect; and
- b) a pharmaceutically acceptable carrier.

2. The diagnostic, therapeutic or radiotherapeutic composition of claim 1 wherein said folate receptor binding ligand has the structure of formula II:

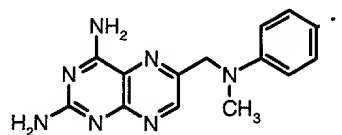


II

wherein R₀ is a folate-receptor binding residue of formula:



or



each X is independently -O-, -S-, -NH-, or -NR₁-;

n₁ is 0 or 1;

b₁ is 1 to 3;

m₁ is 1 to 81;

each K₁ is independently

- a) a macrocyclic or non-macrocyclic metal-chelating ligand radical that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M₁,

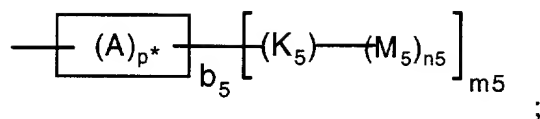
or

- b) a chemotherapeutic drug;

-K₂ is -H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl,

-CON(R₂)₂, -glutamate, -polyglutamate, or -K₃;

-K₃ is



wherein

-K₅ is either

- a) a macrocyclic or non-macrocyclic metal-chelating ligand that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M₅, or
- b) a chemotherapeutic drug

n₅ is 0 or 1;

b₅ is 1 to 3;

m₅ is 1 to 81;

-(A)_p- and -(A)_p*- are each independently optional linkers comprising a straight or branched chain wherein the moieties "A" are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<-, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-, -

CS-, $\text{---} \overset{\text{H}}{\underset{|}{\text{C}}} \text{---}$, $\text{---} \overset{\text{H}}{\underset{|}{\text{C}}} \text{---}$, $\text{---} \overset{\text{H}}{\underset{|}{\text{N}}} \text{---}$, and

p and p* are independently 0 to 24,

or -X-[(A)_p]- and -X-[(A)_p*]- may each independently be the group -Q-

wherein -Q- is -[C(R')(R'')]s₁-[C(t)(R₂₁)]s₂--[C(R₂₂)(R₂₃)]s₃-X₃-Y-

X₄-;

wherein

each s₁, s₂, s₃, and s₄ is independently 0 to 2;

each X₃, X₄, X₅, and X₆ is independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y₁ wherein,

Y₁ is -C(=X₅)-X₆-W-, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉))OH, -P(O)(OR₃₀))OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄, -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

each R' and R'' is independently a single bond, H, alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

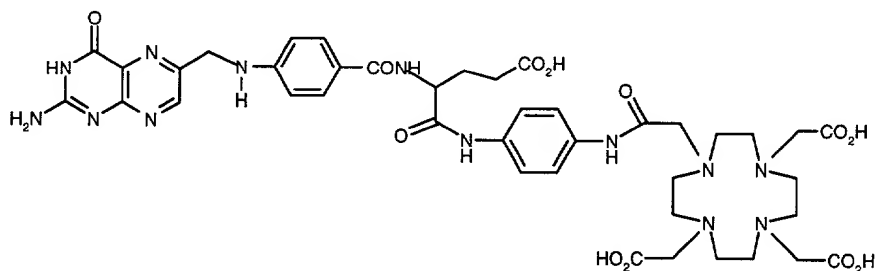
each R₃ through R₅, R₇, R₈, R₂₁ through R₂₃, and R₂₅ through R₂₇ is independently H, alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

each R₁, R₂, R₆, R₉ through R₁₂, R₂₄, and R₂₈ through R₃₇ is independently H, alkyl,

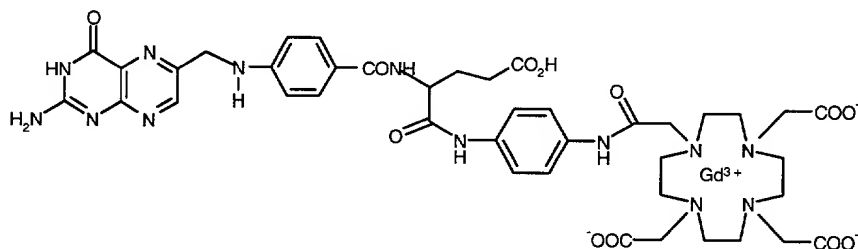
alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle;
or a pharmaceutically acceptable salt thereof.

3. The composition of claim 2 for use in nuclear medicine or magnetic resonance imaging applications wherein K_1 of the compounds of formula II is a macrocyclic or non-macrocyclic metal-chelating ligand that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M_1 , and K_2 is other than K_3 .

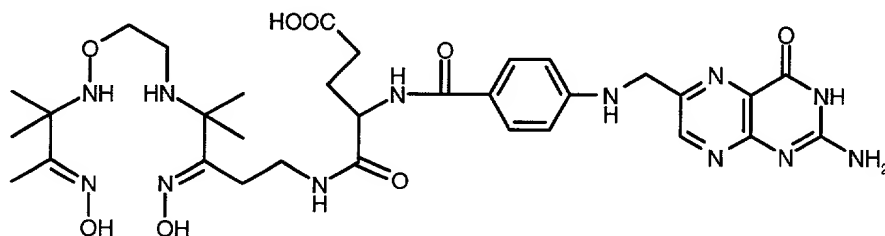
4. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand has the structure:



5. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand has the structure:

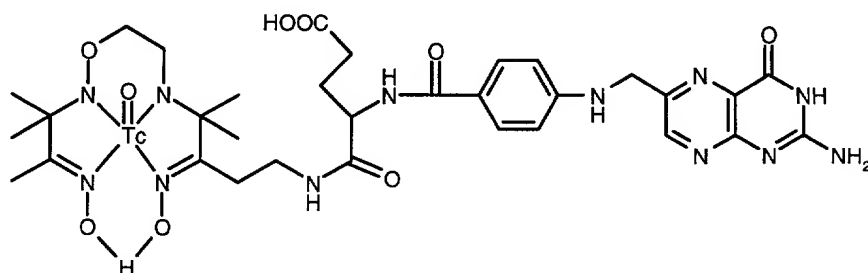


6. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand, 12-N-(N-Pteroyl-(α)-L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime has the structure:

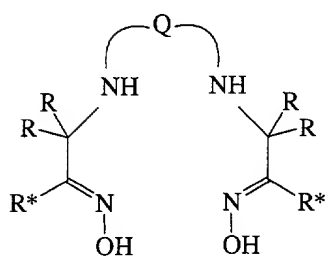


7. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand, Technetium oxo-12-N-(N-Pteroyl-(α)-L-glutamyl)-3,3,9,9-

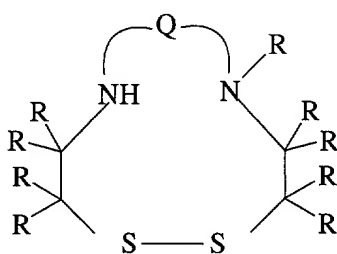
tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime has the structure:



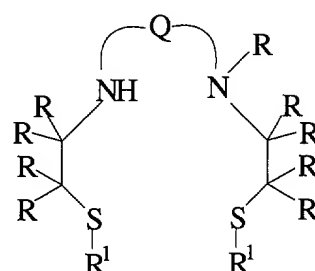
8. The composition of claim 2 wherein
 5 b1 = 1 to 3;
 m1 = 1;
 K₂ is other than K₃; and
 K₁ is a metal chelating ligand radical of formula **IIIa – IIIc**:



IIIa



IIIb



IIIc

wherein

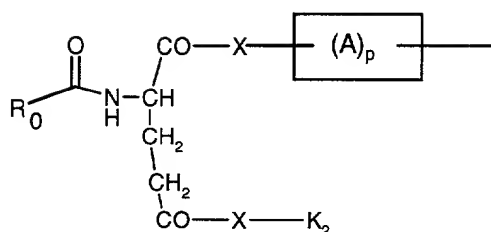
Q is the group $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,
 wherein

Y¹ and Y² are independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4,
 provided that the sum of m1 and m2 is greater than zero;

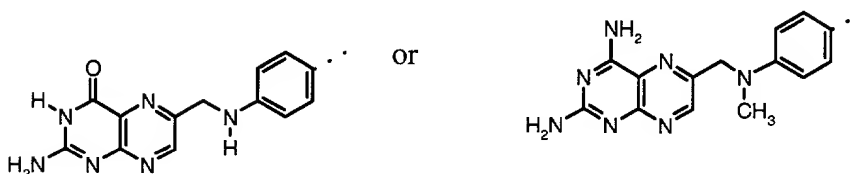
all R and R* groups are independently $-R^2$, $-Cl$, $-F$, $-Br$, $-OR^2$, $-COOR^2$, $-CON(R^2)_2$, $-N(R^2)_2$, $-alkyl-COOR^2$, $-alkyl-C(O)-N(R^2)_2$, $-alkyl-N(R^2)_2$, $-C(O)-OR^2$, $-C(O)-N(R^2)_2$, $-aryl-N(R^2)_2$, acyl; acyloxy; heterocyclo; hydroxyalkyl; $-SO_2-R^2$; $-alkyl-SO_2-R^2$; or $-$

R³, wherein $-R^3$ is a folate-receptor binding residue of formula **IV**; or
 two R groups, or an R group and an R* group, taken together with the one or more atoms to
 which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic
 (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or
 substituted by one or more groups R or R* groups above,
 with the proviso that a carbon atom bearing an R group is not directly bonded to more than
 one heteroatom; and that one to three of R or R* is, or contains a folate-receptor
 binding radical $-R^3$ of formula **IV**:



IV

wherein R_0 is a folate-receptor binding residue of formula:



each X is independently -O-, -S-, -NH- or -N(R₂)-;

K_2 is -H-, alkyl-, alkenyl-, alkynyl-, alkoxy-, aryl-, alkyl-, -CON(R₂)₂-, glutamate-, or -polyglutamate;

-(A)_p- is an optional linker comprising a straight or branched chain wherein the moieties "A" are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈-, >C=C<-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-

, -CS-, $\begin{smallmatrix} | \\ -C- \\ | \end{smallmatrix}$, $\begin{smallmatrix} H \\ | \\ -C- \\ | \end{smallmatrix}$, $\begin{smallmatrix} H \\ | \\ -N- \\ | \end{smallmatrix}$, and

p and p* are independently 0 to 24,

R^1 is hydrogen, a thiol protecting group, or the group -R³ defined above;

R_2 is independently hydrogen, alkyl, cycloalkyl, hydroxyalkyl, aryl, or arylalkyl;

R_3 through R_8 are independently hydrogen, alkyl, alkoxy, hydroxy, or aryl;

R^2 and R_9 through R_{12} are independently hydrogen, alkyl, or aryl;

or a pharmaceutically acceptable salt thereof.

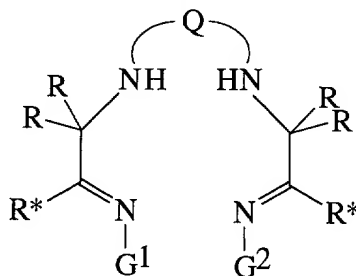
9. The composition of claim 2 wherein

b1 = 1 to 3;

m1 = 1;

K_2 is other than K_3 ; and

K_1 is a metal chelating ligand radical of formula V:



V

wherein

Q is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are independently 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and R^* group is independently: R^1 , -alkoxy, -hydroxy, -halogen, especially fluoro, -haloalkyl, $-OR^1$, $-C(O)-R^1$, $-C(O)-N(R^1)_2$, $-N(R^1)_2$, $-N(R^1)-COR^1$, -alkyl- $C(O)-OR^1$, -alkyl- $C(O)-N(R^1)_2$, -alkyl- $N(R^1)_2-$, -alkyl- $N(R^1)-COR^1$, -aryl- $C(O)-OR^1$, -aryl- $C(O)-N(R^1)_2$, aryl- $N(R^1)_2-$, -aryl- $N(R^1)-COR^1$, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, alkoxyalkyl, hydroxyaryl, arylalkyl, $-SO_2-R^1$, -alkyl- SO_2-R^1 , or $-R^3$, wherein $-R^3$ is a folate-receptor binding residue of formula IV; or

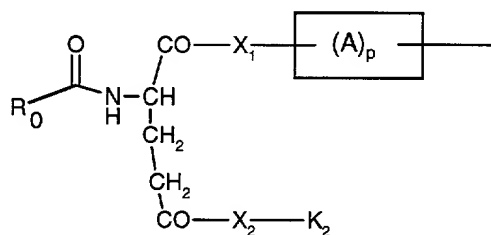
two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

each R^1 is independently hydrogen, alkyl, alkenyl, alkynyl or aryl; and

each G^1 and G^2 is each independently $-OH$ or $-(NR^2)_2$;

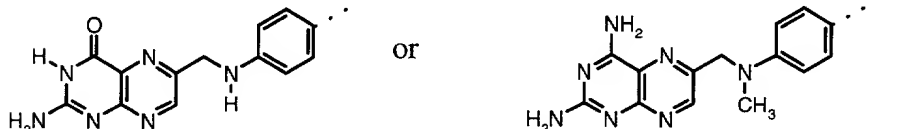
with the proviso that at least one of G^1 or G^2 is $-(NR^2)_2$, where each R^2 is independently hydrogen, alkyl, aryl, acyl or $-R^3$;

and one to three of R, R^* , or R^2 is, or contains a folate-receptor binding radical $-R^3$ of formula IV:



IV

wherein R_0 is a folate-receptor binding residue of formula:



each X is independently $-O-$, $-S-$, $-NH-$ or $-N(R_2)-$;

K_2 is $-H$, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, $-CON(R_2)_2$, -glutamate, or -polyglutamate; wherein R_2 is independently hydrogen, alkyl, or aryl;

A is a linking group as defined in claim 1; and p is 0 to 24;

or a salt thereof.

10. The composition of claim 2 wherein

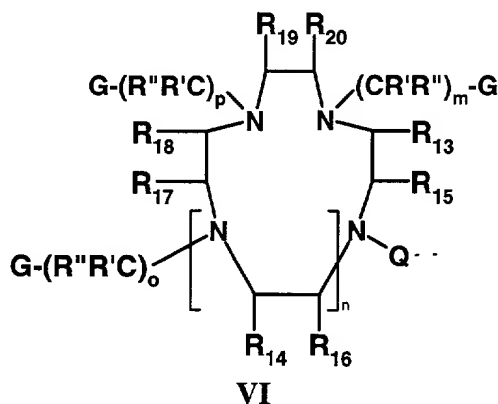
b_1 is 1;

$m_1 = 1$;

$-K_2$ is other than $-K_3$;

5 $-X-[(A)p]-$ is, in its entirety, the group $-Q-$ as defined below;

$-K_1$ is a macrocyclic ligand radical of formula VI:



wherein

n is 0 or 1;

10 each m , o , and p is independently 1 or 2;

$-Q-$ is $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$; wherein

$s1$, $s2$, $s3$, and $s4$ are independently 0 to 2;

$X3$, $X4$, $X5$, and $X6$ are independently a single bond, $-O-$, $-S-$, or $-N(R_{24})-$;

15 Y is a single bond, $-C(R_{25})(R_{26})-$, or $Y1$,

wherein

$Y1$ is $-C(=X5)-X6-W-$, wherein

W is a single bond, $-alkylidene-$, $-cycloalkylidene-$, $-arylidene-$, $-alkenylidene-$, or $-alkynylidene-$, whose carbon atoms may or may not be substituted;

20 t is H , R_{27} , $-C(O)OR_{28}$, $-P(O)(OR_{29})OH$, $-P(O)(OR_{30})OR_{31}$,

$-P(O)(OR_{32})R_{33}$, $-P(O)(OH)R_{34}$, $-C(O)N(R_{35})(R_{36})$, or $C(O)NH(R_{37})$;

each G is independently $-C(O)OR''$, $-P(O)(OR''')OH$, $-P(O)(OR''')_2$,

$-P(O)(OR''')R''$, $-P(O)(OH)R''$, $-C(O)N(R''')_2$, or $C(O)NH(R''')$;

25 each R' and R'' is independently a single bond, H , alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

each R''' is independently a H , alkyl, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

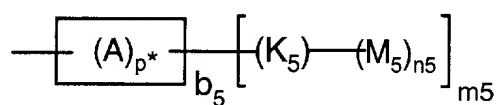
each R_{13} through R_{23} , and R_{25} through R_{27} is independently H , alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

30 each R_{24} , and R_{28} through R_{37} is independently H , alkyl, alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with the carbon atoms in the polyazamacrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;

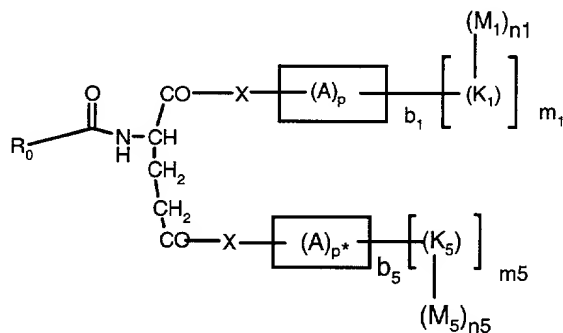
or a pharmaceutically acceptable salt thereof.

11. The composition of claim 2 wherein
-K₂ is



and both -K₁ and -K₅ are macrocyclic or non-macrocyclic metal chelates that are each optionally chelated to radioactive, nonradioactive, paramagnetic or superparamagnetic metals M₁ or M₅.

12. The composition of claim 11 for use in nuclear medicine or magnetic resonance imaging applications comprising a folate-receptor binding ligand of formula IIa:



IIa

wherein

b₁ and b₅ = 1;

m₁ and m₅ = 1;

M₁ and M₅ are independently paramagnetic, superparamagnetic or radioactive metals;

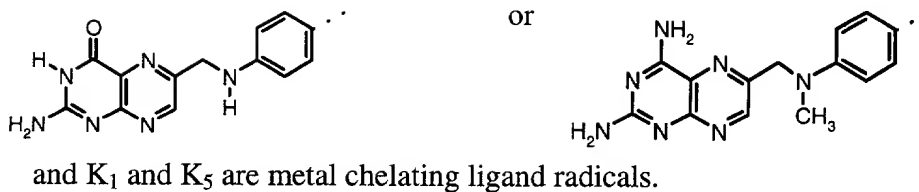
n₁ and n₂ are independently = 0 or 1;

X is -O-, -S-, or -NR²-;

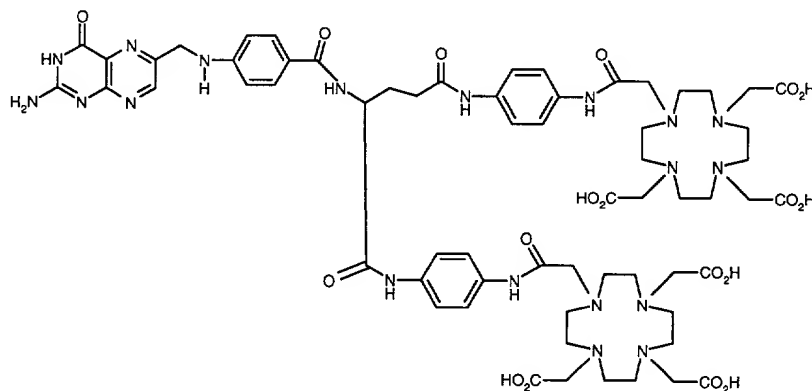
-R² is -hydrogen, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -arylalkyl;

-[(A)p]- and -[(A)p*]- are optional linking groups;

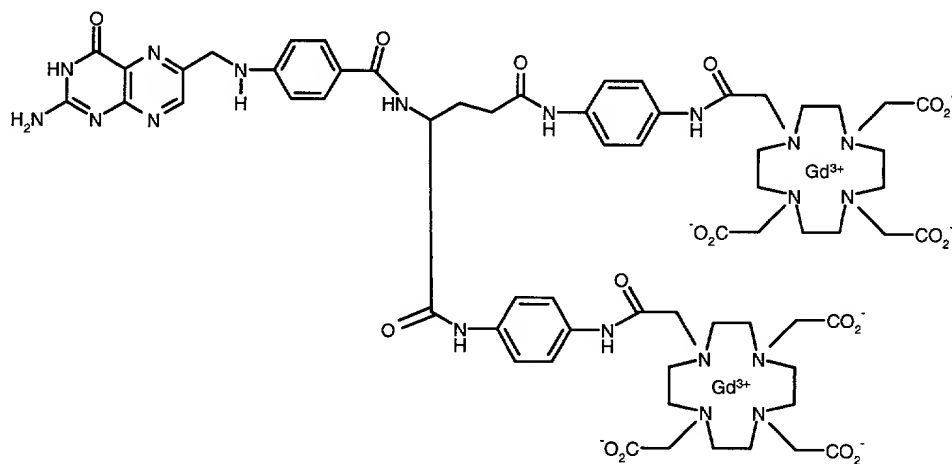
R₀ is a folate-receptor binding residue of formula:



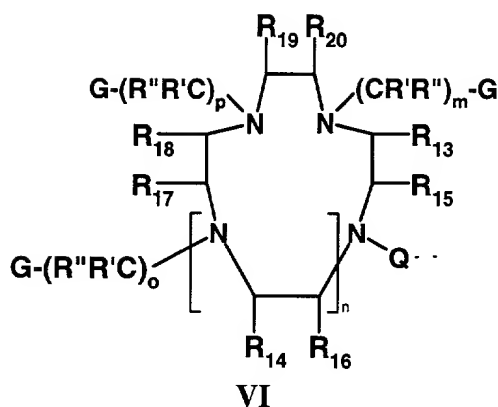
13. The composition of claim **11** wherein said folate receptor binding ligand has the structure:



14. The composition of claim **11** comprising the folate receptor binding ligand Bis (Gd-DO3A-APA)-folate having the structure:



15. The composition of claim **11** wherein both -X-[(A)p]-K₁ and -X-[(A)p*]-K₅ are each in their entirety, macrocyclic ligand radicals of formula **VI**:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is $-\text{C}(\text{R}')(\text{R}'')_{s1}-[\text{C}(\text{t})(\text{R}_{21})]_{s2}-[\text{C}(\text{R}_{22})(\text{R}_{23})]_{s3}-\text{X3}-\text{Y}-\text{X4}-$;

5 wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y1;

wherein

10 Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is -H, -R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉))OH, -P(O)(OR₃₀))OR₃₁,

15 -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄ -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')₂, or C(O)NH(R'');

each R' and R'' is independently a single bond, H, alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

20 each R''' is independently a H, alkyl, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

each R₁₃ through R₂₃, and R₂₅ through R₂₇ is independently H, alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

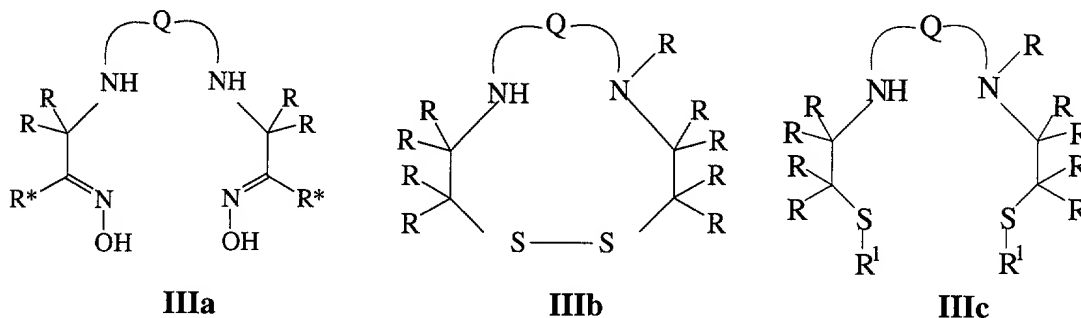
25 each R₂₄, and R₂₈ through R₃₇ is independently H, alkyl, alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic

cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;
or a pharmaceutically acceptable salt thereof.

5

16. The compositions of claim 11 wherein -[(A)p]-K₁ and -[(A)p*]-K₅ are each in their entirety, polydentate ligands radicals of formula **IIIa - IIIc**:



10

wherein

Q is the group $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,

wherein

Y^1 and Y^2 are independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n is 0 or 1; and m₁, m₂ and m₃ are integers independently selected from 0 to 4, provided that the sum of m₁ and m₂ is greater than zero;

15

all R and R* groups are independently $-R^4$, $-Cl$, $-F$, $-Br$, $-OR^5$, $-COOR^5$, $-CON(R^5)_2$, $-N(R^5)_2$, $-alkyl-COOR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-aryl-N(R^5)_2$, acyl, acyloxy, heterocyclo, hydroxyalkyl, $-SO_2-R^5$, $-alkyl-SO_2-R^5$; or $-R^3$;

20

wherein

each $-[R^3]-$ is, in its entirety, the linking group $-[(A)p]-$ or $-[(A)p*]-$ that serves to couple the metal chelating ligand radical to $-X-$;

each $-R^4$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

25

each $-R^5$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted;

with the provisos that a carbon atom bearing an R group is not directly bonded to more than one heteroatom; and

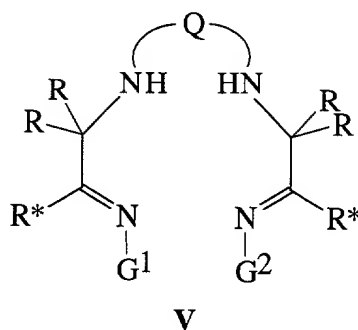
30

at least one R or R* group on each -K₁ and -K₅ is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.

35

17. The composition of claim 11 wherein both $-K_1$ and $-K_5$ are metal-chelating ligand radicals of formula V:



wherein

$-Q-$ is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR^5-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are independently 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each $-R$ and $-R^*$ group is independently: $-R^4$; $-alkoxy$; $-hydroxy$; $-halogen$, especially fluoro; $-haloalkyl$; $-OR^5$; $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$; $-alkyl-C(O)-OR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-alkyl-N(R^5)-COR^5$; $-aryl-C(O)-OR^5$, $-aryl-C(O)-N(R^5)_2$, $-aryl-N(R^5)_2$, $-aryl-N(R^5)-COR^5$, $-nitrile$, $-acyl$, $-acyloxy$, $-heterocyclo$, $-hydroxyalkyl$, $-alkoxyalkyl$, $-hydroxyaryl$, $-arylalkyl$, $-SO_2-R^5$, $-alkyl-SO_2-R^5$, or $-[R^3]-$

wherein

each $-[R^3]-$ is, in its entirety, the linking group $-(A)_p-$ or $-(A)_p^*-$ that serves to couple the metal chelating ligand radical $-K_1$ or $-K_5$ to $-X-$;

each $-R^4$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R^5$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is optionally substituted;

or

two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

each G^1 and G^2 is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of G^1 or G^2 is $-(NR^6)_2$, where each R^6 is independently hydrogen, alkyl, aryl, acyl or $-[R^3]-$; and

A is a linking group; and p is 0 or a positive integer;

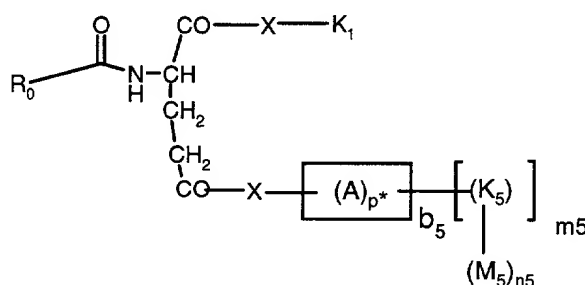
with the proviso that at least one R, R^* , or R^6 group is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.

18. A diagnostic, therapeutic or radiotherapeutic composition for visualization, therapy or radiotherapy of tissues or organs that overexpress folate-binding protein using nuclear medicine, magnetic resonance imaging or neutron capture radiotherapy applications comprising:

- 5 a) a folate-receptor binding ligand and
 b) a pharmaceutically acceptable carrier

wherein said folate-receptor binding ligand has the structure of formula **IIb**:



IIb

10 wherein

-K₁ is -H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate, or -polyglutamate;

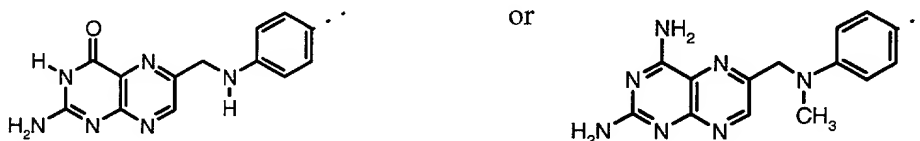
-K₅ is a polydentate metal chelating ligand;

M₅ is a radioactive, paramagnetic or superparamagnetic metal;

15 each -X- is independently -O-, -S-, -NH-, or -NR₁-;

b₅ = 1 to 3, m₅ = 1; n₅ is 0 or 1;

-R₀ is a folate-receptor binding residue of formula:



20 each -[(A)_{p*}]- is an optional linker independently comprising a straight or branched chain made up of "p*" individual (A) moieties that are the same or different and are selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<-, >C=C<-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -

25 HC=N-, -CR₁₁=N-, -NR₁₂-, -CS-, and $\begin{array}{c} \text{H} \\ | \\ -\text{C}- \\ | \end{array}$, $\begin{array}{c} \text{H} \\ | \\ -\text{C}- \\ | \end{array}$, $\begin{array}{c} \text{H} \\ | \\ -\text{N}- \\ | \end{array}$;

and p* is 0 to 24;

or -X-[(A)_{p*}]- is, in its entirety, the group -Q-
 wherein

-Q- is $-\text{C}(\text{R}')(\text{R}'')_{s1}-\text{C}(\text{t})(\text{R}_{21})_{s2}-\text{C}(\text{R}_{22})(\text{R}_{23})_{s3}-\text{X3}-\text{Y}-\text{X4}-$;

wherein

$s1, s2, s3,$ and $s4$ are independently 0 to 2;

$\text{X3}, \text{X4}, \text{X5},$ and X6 are independently a single bond, $-\text{O}-, -\text{S}-,$ or $-\text{N}(\text{R}_{24})-$;

Y is a single bond, $-\text{C}(\text{R}_{25})(\text{R}_{26})-$, or $-\text{Y1}-$

wherein,

Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$, wherein

W is a single bond, $-\text{alkylidene}-, -\text{cycloalkylidene}-, -\text{arylidene}-, -\text{alkenylidene}-,$
or $-\text{alkynylidene}-$, whose carbon atoms may or may not be substituted;

t is $\text{H}, \text{R}_{27}, -\text{C}(\text{O})\text{OR}_{28}, -\text{P}(\text{O})(\text{OR}_{29})\text{OH}, -\text{P}(\text{O})(\text{OR}_{30})\text{OR}_{31},$

$-\text{P}(\text{O})(\text{OR}_{32})\text{R}_{33}, -\text{P}(\text{O})(\text{OH})\text{R}_{34}, -\text{C}(\text{O})\text{N}(\text{R}_{35})(\text{R}_{36}),$ or $\text{C}(\text{O})\text{NH}(\text{R}_{37})$;

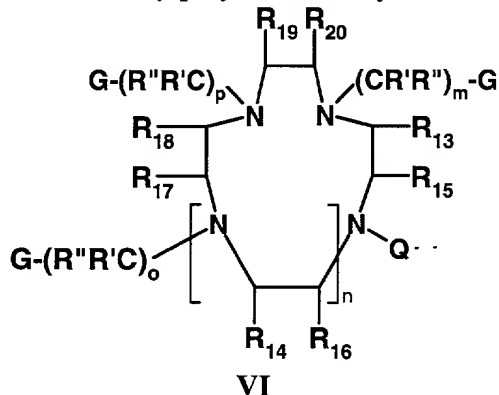
each $-\text{R}'$ and $-\text{R}''$ is independently a single bond, $-\text{H}, -\text{alkyl}, -\text{alkoxy}, -\text{cycloalkyl}, -$
 $\text{hydroxyalkyl}, -\text{aryl},$ or $-\text{heterocyclo},$ each of which is optionally substituted,

each $-\text{R}_3$ through $-\text{R}_5, -\text{R}_7, -\text{R}_8, -\text{R}_{21}$ through $-\text{R}_{23},$ and $-\text{R}_{25}$ through $-\text{R}_{27}$ is
independently $-\text{H}, -\text{alkyl}, -\text{alkoxy}, -\text{halogen}, -\text{hydroxy}, -\text{cycloalkyl}, -\text{hydroxyalkyl}, -$
 $\text{aryl},$ or $-\text{heterocyclo},$ each of which is optionally substituted;

each $-\text{R}_1, -\text{R}_2, -\text{R}_6, -\text{R}_9$ through $-\text{R}_{12}, -\text{R}_{24},$ and $-\text{R}_{28}$ through $-\text{R}_{37}$ is independently $-\text{H}, -$
 $\text{alkyl}, -\text{alkenyl}, -\text{cycloalkyl}, -\text{aryl},$ or a 5- or 6-membered nitrogen or oxygen
containing heterocycle;

or a pharmaceutically acceptable salt thereof.

19. The composition of claim 18 wherein M_5 is a paramagnetic or superparamagnetic metal and $-\text{K}_5$ is an enhanced relaxivity polyaza macrocyclic radical of formula VI:



wherein

n is 0 or 1;

each $m, o,$ and p is independently 1 or 2;

-Q- is $-\text{C}(\text{R}')(\text{R}'')_{s1}-\text{C}(\text{t})(\text{R}_{21})_{s2}-\text{C}(\text{R}_{22})(\text{R}_{23})_{s3}-\text{X3}-\text{Y}-\text{X4}-$;

wherein

$s1, s2, s3,$ and $s4$ are independently 0 to 2;

$\text{X3}, \text{X4}, \text{X5},$ and X6 are independently a single bond, $-\text{O}-, -\text{S}-,$ or $-\text{N}(\text{R}_{24})-$;

Y is a single bond, $-\text{C}(\text{R}_{25})(\text{R}_{26})-$, or Y1

wherein Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$,

wherein W is a single bond, $-\text{alkylidene}-, -\text{cycloalkylidene}-, -$

arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is -H, -R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉)OH, -P(O)(OR₃₀)OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄ - C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);
each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')₂, or C(O)NH(R'');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

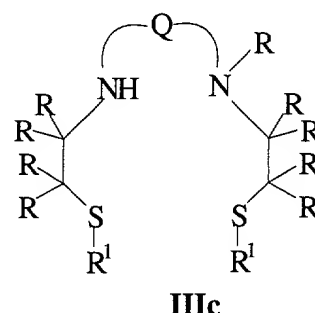
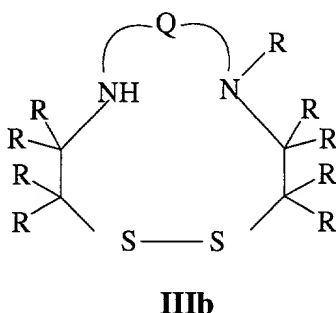
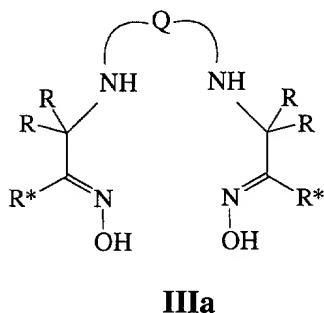
each -R₁₃ through -R₂₃, and R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;

or a pharmaceutically acceptable salt thereof.

20. The compositions of claim 18 wherein -K₅ is a metal chelating polydentate ligand radical of formula IIIa - IIIc:



wherein

Q is the group $-(C(RR))_{m1}-Y^1(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n-}$,

wherein

Y^1 and Y^2 are independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

5 n is 0 or 1; and $m1$, $m2$ and $m3$ are integers independently selected from 0 to 4, provided that the sum of $m1$ and $m2$ is greater than zero;

all R and R* groups are independently $-\text{R}^4$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OR}^5$, $-\text{COOR}^5$, $-\text{CON}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{alkyl-COOR}^5$, $-\text{alkyl-C(O)-N}(\text{R}^5)_2$, $-\text{alkyl-N}(\text{R}^5)_2$, $-\text{C(O)OR}^5$, $-\text{C(O)N}(\text{R}^5)_2$, $-\text{aryl-N}(\text{R}^5)_2$, acyl, acyloxy, heterocyclo, hydroxyalkyl, $-\text{SO}_2-\text{R}^5$, $-\text{alkyl-SO}_2-\text{R}^5$, or $[\text{R}^3]-$;

10 wherein each $[\text{R}^3]-$ is, in its entirety, the linking group $-\text{[(A)p*]}-$ that serves to couple the metal chelating ligand radical $-\text{M}_5$ to $-\text{X}-$;

each $-\text{R}^4$ is independently $-\text{H}$, $-\text{alkyl}$, $-\text{alkoxy}$, $-\text{hydroxy}$, $-\text{cycloalkyl}$, $-\text{hydroxyalkyl}$, $-\text{aryl}$, or $-\text{heterocyclo}$, each of which is optionally substituted;

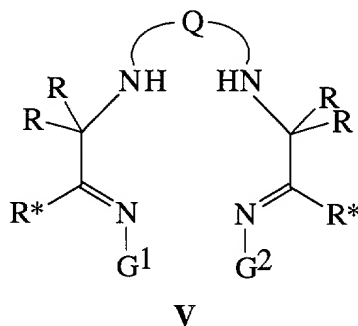
15 each $-\text{R}^5$ is independently $-\text{H}$, $-\text{alkyl}$, $-\text{aryl}$, $-\text{cycloalkyl}$ or $-\text{hydroxyalkyl}$, each of which is independently substituted;

with the provisos that a carbon atom bearing an $-\text{R}$ group is not directly bonded to more than one heteroatom; and that one to three R or R* groups on $-\text{K}_5$ is $-\text{[R}^3]-$;

20

or a pharmaceutically acceptable salt thereof.

21. The compositions of claim 18 wherein $-\text{K}_5$ is a polydentate metal-chelating ligand radical of formula V:



25

wherein

Q is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are independently 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

30

each R and R* group is independently: $-\text{H}$, $-\text{R}^4$; $-\text{alkoxy}$; $-\text{hydroxy}$; $-\text{halogen}$, especially fluoro, $-\text{haloalkyl}$, $-\text{OR}^5$, $-\text{C(O)-R}^5$, $-\text{C(O)-N}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)-$

COR⁵, -alkyl-C(O)-OR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂-, -alkyl-N(R⁵)-COR⁵, -aryl-C(O)-OR⁵, -aryl-C(O)-N(R⁵)₂, -aryl-N(R⁵)₂-, -aryl-N(R⁵)-COR⁵, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, -arylalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

each -[R³]- is, in its entirety, the linking group -[(A)p*]- that serves to couple the metal chelating ligand radical -K₅ to -X-;

each -R⁴ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R⁵ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

or

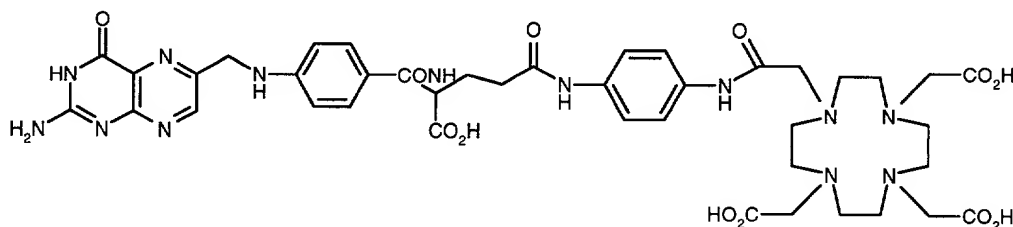
two R groups, or an R group and an R* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R* groups above;

each -G¹ and -G² is independently -OH or -(NR⁶)₂; with the proviso that at least one of -G¹ or -G² is -(NR⁶)₂, where each -R⁶ is independently -hydrogen, -alkyl, -aryl, -acyl or -[R³]-; and

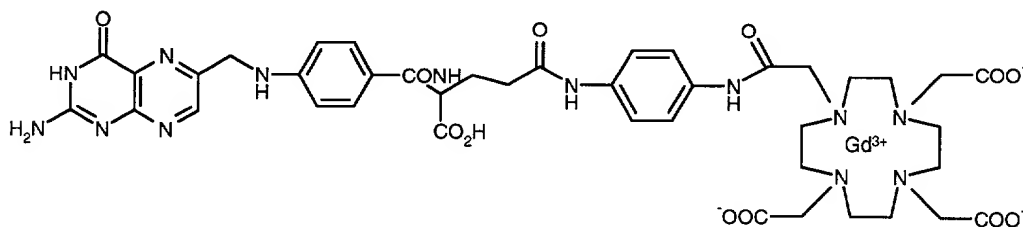
A is a linking group; and p is 0 or a positive integer;

with the proviso that at one to three -R, -R*, or -R⁶ groups is -[R³]-; or a pharmaceutically acceptable salt thereof.

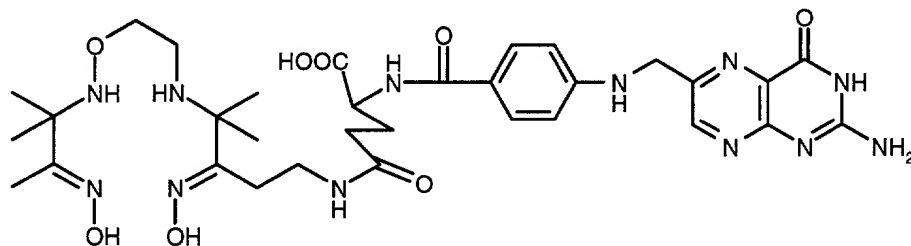
22. The composition of claim 18 wherein said folate-receptor binding ligand, N-Pteroyl-γ-glutamyl-APADO3A, has the structure:



23. The composition of claim 18 containing the folate-receptor binding ligand Gd-DO3A-APA-(γ)-folate, having the structure:



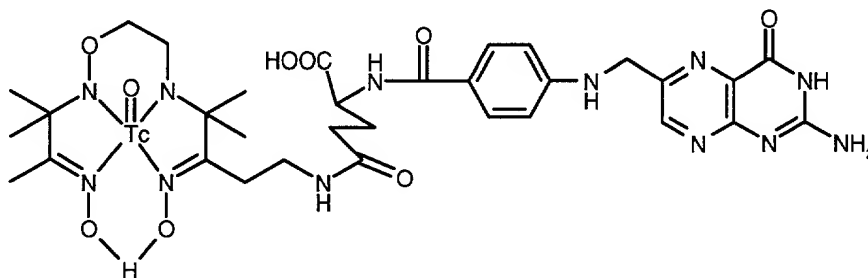
24. The composition of claim **18** containing the folate-receptor binding ligand 12-N-(N-Pteroyl- γ -L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime, having the structure:



5

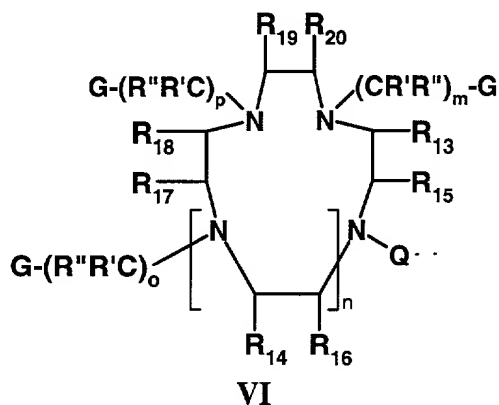
25. The composition of claim **18** containing the folate-receptor binding ligand Technetium oxo 12-N-(N-Pteroyl- γ -L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime, having the structure:

10



26. The composition of claim **18** wherein M_1 or both M_1 and M_5 are paramagnetic or superparamagnetic metals and K_1 or both $-K_1$ and $-K_5$ are enhanced relaxivity polyaza macrocyclic radicals of formula **VI**:

15



wherein

n is 0 or 1;

each m , o , and p is independently 1 or 2;

Q is $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$;

wherein

20

s1, s2, s3, and s4 are independently 0 to 2;
 Y is a single bond, -C(R25)(R26)-, or Y1 wherein,
 Y1 is -C(=X5)-X6-W-, wherein

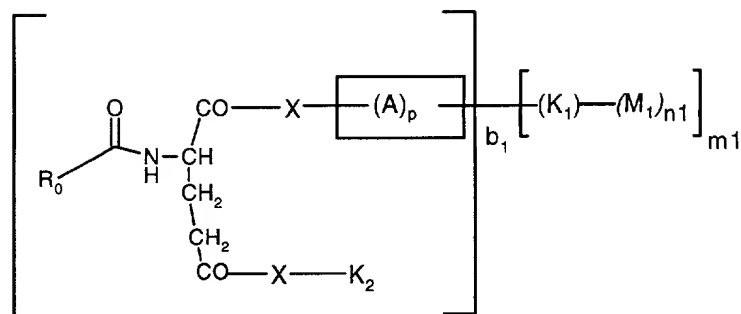
W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R27, -C(O)OR28, -P(O)(OR29))OH, -P(O)(OR30))OR31, -P(O)(OR32)R33, -P(O)(OH)R34 -C(O)N(R35)(R36), or C(O)NH(R37);
 each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')2, -P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')2, or C(O)NH(R'');
 each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,
 each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,
 each -R13 through -R23, and -R25 through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;
 each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with R18, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R13, together with R15, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R17 and R18 are hydrogen;

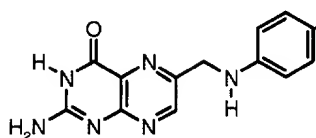
or a pharmaceutically acceptable salt thereof.

27. The composition for visualization or radiotherapy of tissues or organs that overexpress folate-binding protein using magnetic resonance imaging or neutron capture therapy techniques comprising one or more folate-receptor binding residues conjugated to one or more enhanced relaxivity polyaza macrocyclic radicals which are optionally chelated to a paramagnetic or superparamagnetic metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a radiotherapeutic effect using neutron capture therapy; wherein said folate-receptor binding compound has the structure of formula **IIc**:

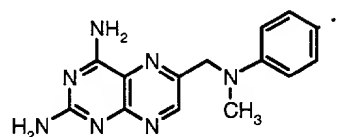
**IIc**

wherein

R₀ is a folate-receptor binding residue of formula:



or



each X is independently -O-, -S-, -NH-, or -NR₁-;

n₁ and n₅ are independently 0 or 1;

b₁ and b₅ are independently 1 to 3;

m₁ and m₅ are independently 1 to 81;

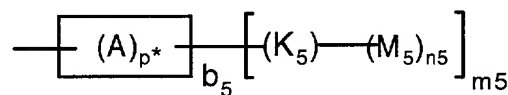
each -K₁ is independently

-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate, -polyglutamate, or -K₄;

each -K₂ is independently

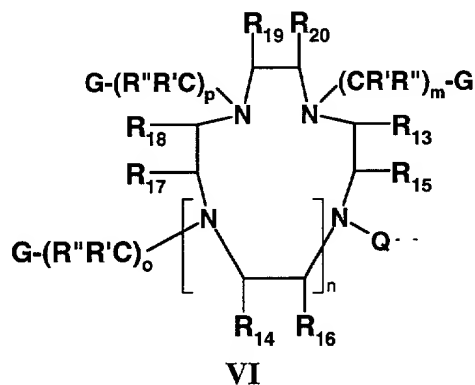
-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate, -polyglutamate, or -K₃;

-K₃ is



M₁ and M₅ are paramagnetic or superparamagnetic metals; and

-K₄ and -K₅ are each independently enhanced-relaxivity polyaza macrocyclic metal-chelating ligand radicals of formula **VI** that are optionally chelated to M₁ and M₅:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is $-\text{C}(\text{R}')(\text{R}'')_{\text{s}1}-\text{C}(\text{t})(\text{R}_{21})_{\text{s}2}-\text{C}(\text{R}_{22})(\text{R}_{23})_{\text{s}3}-\text{X3}-\text{Y}-\text{X4}-$; wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y1,

wherein Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉))OH, -P(O)(OR₃₀))OR₃₁,

-P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄ -C(O)N(R₃₅)(R₃₆), or

C(O)NH(R₃₇);

each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂,

-P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')₂, or C(O)NH(R'');

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R₁₃ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;

-(A)p- and -(A)p*- are optional linkers each independently comprising a straight or branched chain made up of moieties that are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-,

$>CR_7-CR_8<$, $-C=C-$, $-CR_9=CR_{10}-$, $-C\equiv C-$, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ($-CO-$), $-O-$, $-S-$, $-NH-$, $-HC=N-$, $-CR_{11}=N-$,

$-NR_{12}-$, $-CS-$, $-\overset{|}{C}-$, $-\overset{H}{\underset{|}{C}}-$, $-\overset{H}{\underset{|}{N}}-$; and

p and p* are each individually 0 to 24;

5

or $-X-[(A)p]-$ or $-X-[(A)p^*]-$ in its entirety is the group $-Q-$ as defined above

each $-R_3$ through $-R_5$, $-R_7$ and $-R_8$ is independently $-H$, -alkyl, -alkenyl, -alkoxy, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, halogen, hydroxy or -hydroxyalkyl; and

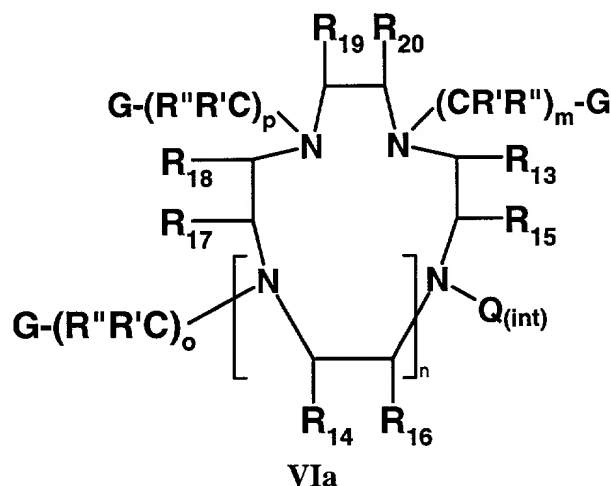
10

each $-R_1$, $-R_2$, $-R_6$, $-R_9$ through $-R_{12}$ is independently $-H$, -alkyl, -alkoxy, -cycloalkyl, -aryl, -heterocyclo-, -hydroxy or -hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

28. A conjugatable polyaza macrocyclic intermediate useful for the preparation of the composition of claim 27, said intermediate containing at least one free amine, carboxylate or thiocarboxylate functionality that can be used for conjugation to targeting vectors such as folate, said intermediates having the structure of formula VIa:

15



wherein

20

n is 0 or 1;

each m, o, and p is independently 1 or 2;

$-Q(int)$ is a conjugatable amine-, carboxylate- or thiocarboxylate-containing group of formula $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X_3-Y-X_4$;

wherein

25

s_1 , s_2 , s_3 , and s_4 are independently 0 to 2;

X_3 is a single bond, $-O-$, $-S-$, $-NH-$ or $-NR_{24}-$ if Y is present,

or X_3 is $-OH$, $-SH$, $-NH_2$ or $-N(R_{24})H$ if Y and X_4 are absent;

X_4 is a single bond, $-OH$, $-COOH$, $-SH$, $-NHR_{24}$ or $-NH_2$;

Y is a single bond, $-C(R_{25})(R_{26})-$, or Y1

30

wherein,

Y1 is $-C(=X_5)-X_6-W-$, wherein

X_5 is =O or =S;

X_6 is a single bond, -SH, -NH(R_{38}), -NH₂
or -OH if W and X_4 are absent, and
is -S-, -O-, -NH-, or -N(R_{39})-, if W and X_4 are
present;

W is a single bond, or is -alkylidene-, -cycloalkylidene-, -arylidene-, -
alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be
substituted;

t is -H, - R_{27} , -C(O)OR₂₈, -P(O)(OR₂₉))OH, -P(O)(OR₃₀))OR₃₁, -P(O)(OR₃₂)R₃₃, -

10 P(O)(OH)R₃₄ -C(O)N(R_{35})(R_{36}), or -C(O)NH(R_{37});

each -G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -
P(O)(OH)R'' -C(O)N(R'')₂, or -C(O)NH(R'');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -
hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

15 each -R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo,
each of which is optionally substituted,

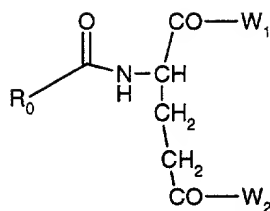
each - R_{13} through - R_{23} , and - R_{25} through - R_{27} is independently -H, -alkyl, alkoxy, -
halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which
is optionally substituted;

20 each - R_{24} , and - R_{28} through - R_{39} is independently -H, -alkyl, -alkenyl, cycloalkyl, aryl,
a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is
optionally substituted;

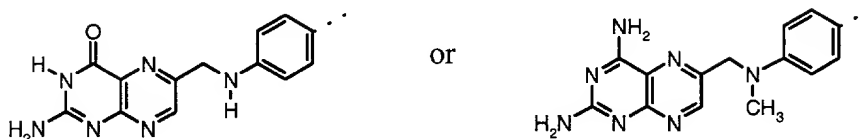
or R_{13} together with R_{15} , and R_{17} together with R_{18} , independently form, together with
the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or
25 partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or
substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and
which may be further fused to a carbocyclic ring, or R_{13} and R_{15} are each hydrogen
and R_{17} , together with R_{18} , forms a fused fully or partially saturated non-aromatic
cyclohexyl ring as defined above, or R_{13} , together with R_{15} , forms a fused fully or
30 partially saturated non-aromatic cyclohexyl ring as defined above, and R_{17} and R_{18} are
hydrogen;

or a pharmaceutically acceptable thereof.

29. A composition comprising folate-receptor binding ligands and a pharmaceutically
35 acceptable carrier for use nuclear medicine, magnetic resonance imaging, or neutron
capture therapy techniques, said folate-receptor binding ligands comprising dendrimeric
first-, second-, third-, and fourth- generation conjugates containing one folate-receptor
binding residue coupled one or more macrocyclic metal-chelating ligand radicals that are
optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive
40 metals capable of either being detected outside the body by imaging means for diagnosis or
capable of providing a therapeutic or radiotherapeutic effect; wherein said folate-receptor
binding compounds have the structure of formulae VIIa – VIId:

**VIIa - VIId**

wherein R_0 is a folate-receptor binding residue of formula:



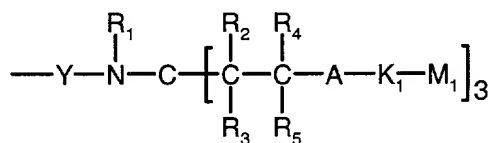
- 5 wherein for the first generation dendrimers of formula **VIIa**, bearing one folate-receptor binding residue and 3 or 6 metal chelating ligand radicals:

W_1 and W_2 are each independently $-\text{OR}''$, $-\text{SR}''$, $-\text{NR}''\text{R}''$, $-\text{CON}(\text{R}_2)_2$, -glutamate, -polyglutamate, or $-\text{K}_6$;

wherein each $-\text{R}''$ is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -

- 10 heterocyclo;

with the proviso that either W_1 , W_2 , or both W_1 and W_2 of formula **VIIa** must be $-\text{K}_6$, where $-\text{K}_6$ is a residue of formula **VIIIa**:

**VIIIa**

wherein

- 15 Y is a single bond or $-\text{Y}'\text{---C}(=\text{X})\text{---}$

wherein

X is =O or =S;

Y' is $\text{N}(\text{R}_6)\text{---Z}$;

wherein

- 20 Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is $-\text{C}(=\text{O})$ -, $\text{C}(=\text{S})$ -, or $-\text{CH}_2\text{---N}(\text{R}_7)\text{---}$;

M_1 is a superparamagnetic, paramagnetic, radioactive or non-radioactive metal, and

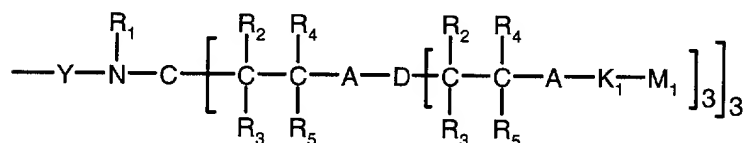
K_1 is a macrocyclic metal chelating ligand residue;

- 25 and,

wherein for second generation dendrimers, bearing one folate receptor binding residue and 9 or 18 macrocyclic metal-chelating ligand radicals and having the structure of formula **VIIIb**:

W_1 and W_2 are each independently $-\text{OR}''$, $-\text{SR}''$, $-\text{NR}''\text{R}''$, or $-\text{K}_7$,

wherein each -R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo, and -K₇ is a residue of formula **VIIIb**; with the proviso that either W₁, W₂, or both W₁ and W₂ must be -K₇

**VIIIb**

wherein

Y is a single bond or -Y'-C(=X)-

wherein X is =O or =S and Y' is -N(R₆)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, C(S)-, or -CH₂-N(R₇)-;

D is -N(R₆)-C- if A is -C(O)- or -C(S)- or -C(=X₂)-E-N(R₇)-C- if A is -CH₂-N(R₇)-;

wherein

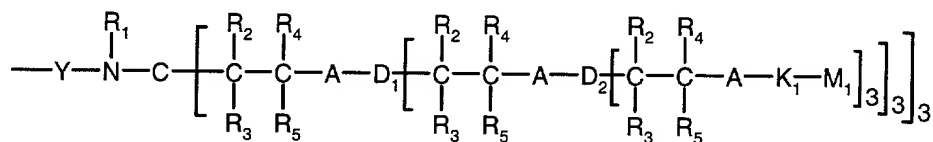
E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S;

and wherein

for the third generation dendrimeric compounds of formula **VIIIc**; bearing one folate receptor binding residue and 27 or 54 macrocyclic metal-chelating ligand radicals:

W₁ and W₂ are each independently -OR''', -SR''', -NR'''R''', or -K₈ wherein each -R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo, and -K₈ is a residue of formula **VIIIc**;

with the proviso that either W₁, W₂, or both W₁ and W₂ of the compounds of formula **VIIIc** must be -K₈ :

**VIIIc**

wherein,

Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R₆)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;

D₁ and D₂ are each independently -N(R₆)-C if A is -C(O)- or -C(S)-, and
-C(=X₂)-E-N(R₇)-C if A is -CH₂-N(R₇)-;

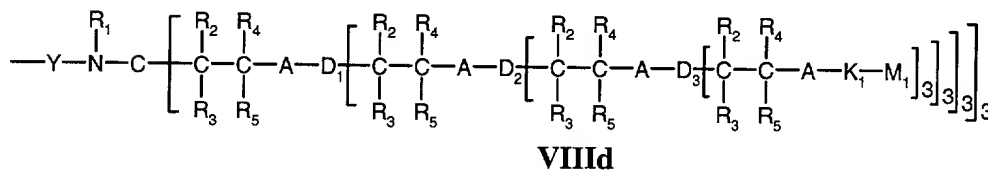
5 wherein

E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S;

and

10 wherein for the fourth generation dendrimeric compounds of formula **VIII_d**; bearing one folate receptor binding residue and 81 or 162 macrocyclic metal-chelating ligand radicals:

15 W₁ and W₂ are each independently -OR''', -SR''', -NR'''R''' or -K₉, wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo and -K₉ is a residue of formula **VIII_d**; with the proviso that either W₁, W₂, or both W₁ and W₂ of the compounds of formula **VIII_d** must be -K₉);



20 wherein Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R₆)-Z-;

wherein

25 Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;

D₁, D₂, and D₃ are each independently -N(R₆)-C if A is -C(O)- or C(S)-, and
-C(=X₂)-E-N(R₇)-C if A is -CH₂-N(R₇)-;

30 wherein E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S; and

each -R₁ to -R₇ of the compounds of formula **VIII_a-VIII_d** is independently -H, -alkyl, -hydroxyalkyl, -alkoxy, -alkoxyalkyl, -cycloalkyl, or -aryl; each of which is optionally substituted,

or a pharmaceutically acceptable salt thereof.

35 30. The composition of claim 29 wherein W₁ of formula **VIII_a - VIII_d** is a residue of formula **VIII_a, VIII_b, VIII_c or VIII_d**;

and

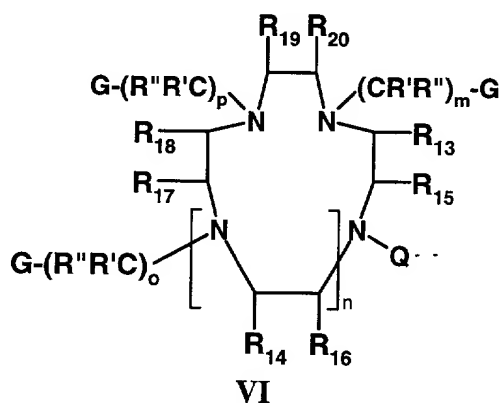
W₂ of formula **VIII_a - VIII_d** is -OR''', -SR''', -NR'''R''' -CON(R₂)₂, -glutamate, or -

polyglutamate, wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo.

31. The composition of claim 29 wherein W₂ of formula VIIa – VIId is a residue of formula VIIa, VIIb, VIIc or VIId;
and W₁ of formula VIIa – VIId is -OR''', -SR''', -NR'''R''' -CON(R₂)₂, -glutamate, or -polyglutamate, wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo.

32. The dendrimeric compositions of claim 29 wherein both W₁ and W₂ of formula VIIa – VIId is a residue of formula VIIa, VIIb, VIIc or VIId.

33. The dendrimeric folate-receptor binding compositions of formula VIIa – VIId of claim 29 for use in diagnostic imaging using magnetic resonance or nuclear medicine techniques, or for use in radiation- or neutron-capture therapy, wherein M₁ is a radioactive-, paramagnetic- or superparamagnetic- metal and each K₁ is a macrocyclic metal chelating ligand radical of formula VI:



wherein said metal chelating radical is attached to the remainder of the compound of formulae VIIa - VIId via the free -N(R)- atom of the function -Q- if A is -C(O)- or -C(S)- or through the free -C(O)- atom of the function -Q- if A is -CH₂-N(R₇)-;

wherein -Q- is -[C(R')(R'')]s₁-[C(t)(R₂₁)]s₂--[C(R₂₂)(R₂₃)]s₃-X₃-Y-X₄-;

wherein

s₁, s₂, s₃, and s₄ are independently 0 to 2;

X₃, X₄, X₅, and X₆ are independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y₁,

wherein Y₁ is -C(=X₅)-X₆-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉))OH, -P(O)(OR₃₀))OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄, -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

each G is independently -C(O)OR^{'''}, -P(O)(OR^{'''})OH, -P(O)(OR^{'''})₂, -P(O)(OR^{'''})R^{''}, -P(O)(OH)R^{''} C(O)N(R^{'''})₂, or C(O)NH(R^{'''});

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

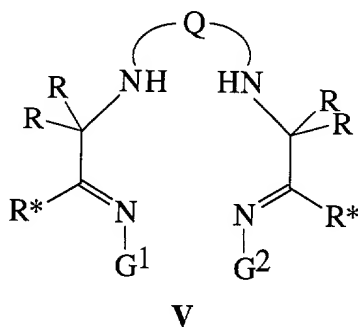
each R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R₁₃ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or a pharmaceutically accepted salt thereof.

34. The dendrimeric folate receptor binding composition of formula VIIa - VIId of claim 29 wherein M₁ is a radioactive metal and at least one -K₁ is a macrocyclic metal chelating ligand radical of formula V:



wherein

-Q- is the group -(C(RR))_{m1}-(Y¹)_n-(C(RR))_{m2}-(Y²-(C(RR))_{m3})_{n1};

Y¹ and Y² are each independently -CH₂-, -NR-, -O-, -S-, -SO-, -SO₂- or -Se-;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that m1 + m2 + n + n1 is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R* group is independently: -R⁴; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl, -OR⁵, -C(O)-R⁵, -C(O)-N(R⁵)₂, -N(R⁵)₂, -N(R⁵)-COR⁵, -alkyl-C(O)-OR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂-, -alkyl-N(R⁵)-COR⁵, -aryl-C(O)-OR⁵, -aryl-C(O)-N(R⁵)₂, aryl-N(R⁵)₂-, -aryl-N(R⁵)-COR⁵, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

-[R³]- is a linking group -[(A)p]- that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae

VIIa through VIId;

wherein $-(A)_p-$ comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: $-\text{CH}_2-$, $-\text{CHR}_3-$, $-\text{CR}_4\text{R}_5-$, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CR}_6-$,
 5 $>\text{CR}_7-\text{CR}_8<$, $-\text{C}=\text{C}-$, $-\text{CR}_9=\text{CR}_{10}-$, $-\text{C}\equiv\text{C}-$, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl $(-\text{CO}-)$, $-\text{O}-$, $-\text{S}-$,

$-\text{NH}-$, $-\text{HC}=\text{N}-$, $-\text{CR}_{11}=\text{N}-$, $-\text{NR}_{12}-$, $(-\text{CS}-)$, $-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{N}}}-$,
 and

p is an integer from 0 to 24;

each $-\text{R}^4$ and $-\text{R}_3$ through $-\text{R}_5$ is independently $-\text{H}$, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each $-\text{R}^5$ and R_6 through R_{12} is independently $-\text{H}$, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

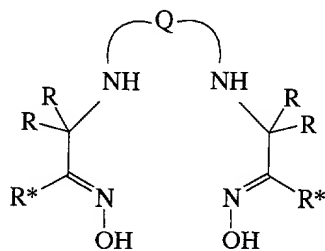
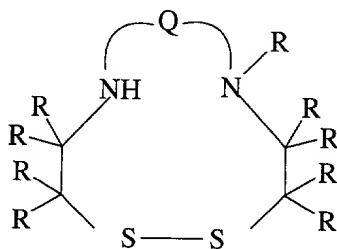
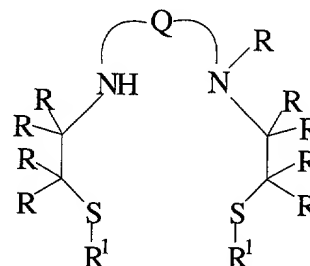
two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

each $-\text{G}^1$ and $-\text{G}^2$ is independently $-\text{OH}$ or $-(\text{NR}^6)_2$; with the proviso that at least one of $-\text{G}^1$ or $-\text{G}^2$ is $-(\text{NR}^6)_2$, and each $-\text{R}^6$ is independently -hydrogen, -alkyl, -aryl, -acyl or $-\text{[R}^3\text{]}-$;

with the proviso that at least one $-\text{R}$, $-\text{R}^*$, or $-\text{R}^6$ group is $-\text{[R}^3\text{]}-$;

or a pharmaceutically acceptable salt thereof.

35. The dendrimeric folate-receptor binding composition of formula **VIIa – VIId** of claim 29 for use in nuclear medicine or radiotherapy wherein M_1 is a radioactive isotope and at least one K_1 is a macrocyclic metal chelating ligand of formula **IIIa - IIIc**:

**IIIa****IIIb****IIIc**

wherein

Q is the group $-(\text{C}(\text{RR}))_{m1}-\text{Y}^1(\text{C}(\text{RR}))_{m2}-(\text{Y}^2-(\text{C}(\text{RR}))_{m3})_n-$,

wherein

Y^1 and Y^2 are independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4, provided that the sum of m1 and m2 is greater than zero;

all R and R* groups are independently -R⁴, -Cl, -F, -Br, -OR⁵, -COOR⁵, -CON(R⁵)₂, -N(R⁵)₂, -alkyl-COOR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂, -C(O)OR⁵, -C(O)N(R⁵)₂, -aryl-N(R⁵)₂, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

- [R³]- is a linking group -[(A)p]- that links the metal chelating ligand of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule; wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl -(CO)-, -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-, and -(CS)-

, $-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{N}}}-$, and

p is an integer from 0 to 24;

each -R⁴ and -R₃ through -R₅ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

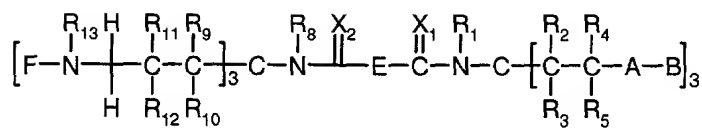
each -R⁵ and -R₆ through R₁₂ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or -R* group on -K₁ is -[R³]-

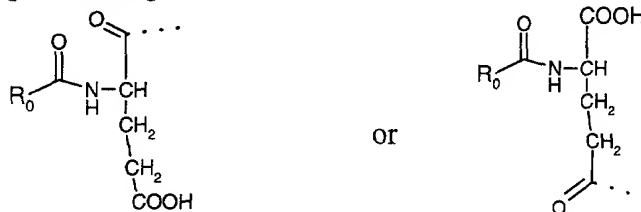
or a pharmaceutically acceptable salt thereof.

36. A folate-receptor binding ligand comprising dendrimeric first-, second-, third-, and fourth- generation conjugates containing one or more folate-receptor binding residues coupled to one or more macrocyclic metal-chelating ligand radicals that are capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect, wherein said folate-receptor binding ligands have the structure of formulae **IXa**, **IXb**, **IXc**, and **IXd**, representing dendrimers of generations 1, 2, 3, and 4, respectively,

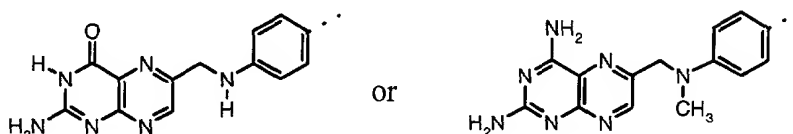
wherein for the first generation dendrimers of formula **IXa**, bearing three folate and three metal chelating ligand radicals;

**IXa**

F is a folate-receptor binding residue of formula:

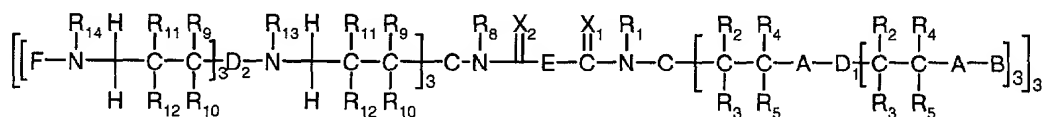


wherein R_0 is a residue of formula:



- 5 each X_1 through X_4 is independently =O or =S;
 each A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;
 E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;
 B is a macrocyclic metal-chelating ligand radical that is attached to A via an
 10 amide or thioamide bond and is optionally chelated to a paramagnetic,
 superparamagnetic, radioactive or non-radioactive metal;
 -R₁, -R₆ through -R₈, -R₁₃, and -R₁₄ are independently -H, -alkyl, -
 hydroxyalkyl, -cycloalkyl, or -aryl;
 -R₂ through -R₅ and -R₉ through -R₁₂ are independently -H, -alkyl, -
 15 hydroxyalkyl, -alkoxy, -hydroxyalkyl, -halogen, -cycloalkyl, -aryl or -
 heterocyclo;
 or a pharmaceutically accepted salt thereof;

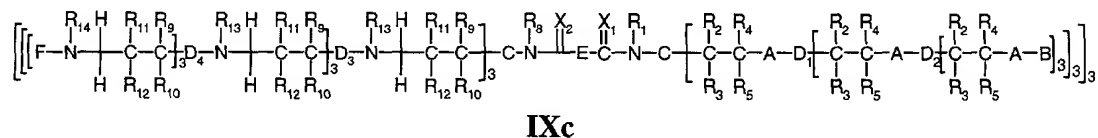
and wherein for the second generation dendrimeric compounds of formula **IXb**, bearing
 20 nine folate-receptor binding residues and nine metal-chelating ligand radicals:

**IXb**

A, B, E, F, X_1 through X_4 and all -R groups are as defined for the compounds
 of formula **IXa**;

D_1 and D_2 are independently -N(R₆)-C if A is -C(O)- or -C(S)-, and -C(=X₃)-
 25 E-N(R₇)-C if A is -CH₂-N(R₇)-;

and wherein for the third generation dendrimeric compounds of formula **IXc**, bearing 27 folate receptor binding residues and 27 metal chelating ligand radicals;



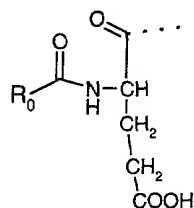
- 5 D₁, D₂, D₃, and D₄ are independently -N(R₆)-C if A is -C(O)- or -C(S)-, and -C(=X₃)-E-N(R₇)-C if A is -CH₂-N(R₇)-; and all other groups are defined as above;

[illegible]

D₁, D₂, D₃, D₄, D₅, and D₆ are each independently -N(R₆)-C if A is -C(O)- or -C(S)-, and -C(=X₃)-E-N(R₇)-C if A is -CH₂-N(R₇)-;

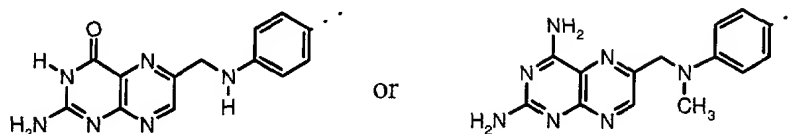
123

37. The dendrimeric composition of claim **36** wherein F of formulae **IXa**, **IXb**, **IXc**, and **IXd** is a folate-receptor binding residue of formula:



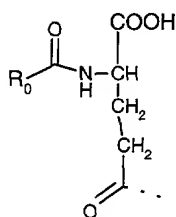
wherein R₀ is a residue of formula:

5

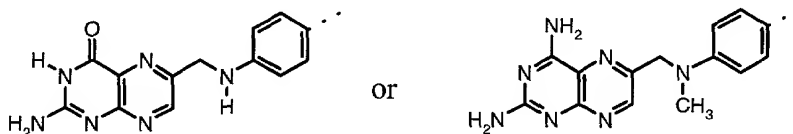


or a pharmaceutically acceptable salt thereof.

10 38. The dendrimeric folate-receptor binding composition of claim **36** wherein F of formulae **IXa**, **IXb**, **IXc**, and **IXd** is a folate receptor binding residue of formula:



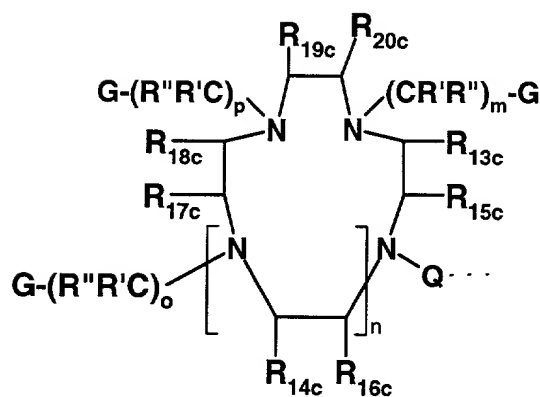
wherein R₀ is a residue of formula:



15

or a pharmaceutically acceptable salt thereof.

20 39. The folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim **36**, wherein B is a polyaza macrocyclic ligand radical of formula **VIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal,



VIc

wherein said macrocyclic ligand radical is attached to A via an amide or thioamide linkage through a free N atom of the function -Q- if A is -C(O)- or -C(S)- or through a free -C(O)- group of the function -Q- if A is -CH₂-N(R₇)-;

-Q- is -[C(R')(R'')]s₁-[C(t)(R₂₁)]s₂-[C(R₂₂)(R₂₃)]s₃-X₃-Y-X₄;

wherein

s₁, s₂, s₃, and s₄ are independently 0 to 2;

-X₃, -X₄, -X₅, and -X₆ are independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y₁,

wherein Y₁ is -C(=X₅)-X₆-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉)OH, -P(O)(OR₃₀)OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄, -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -P(O)(OH)R'', -C(O)N(R'')₂, or -C(O)NH(R'');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

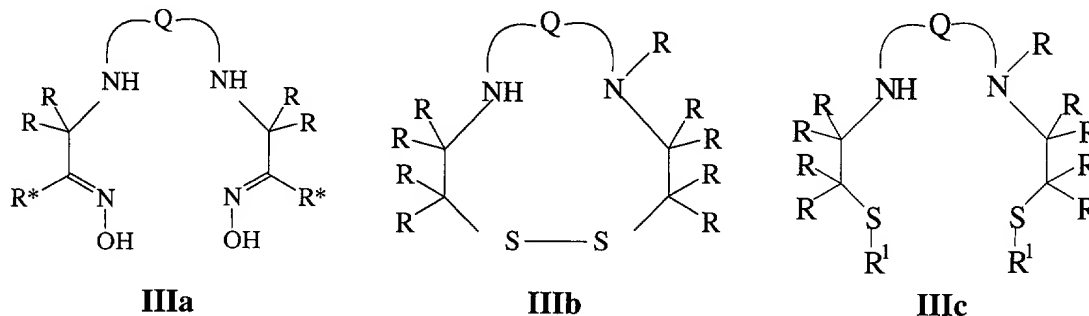
each -R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R_{13c} through -R_{20c}, -R₂₁ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen-containing heterocycle, each of which is optionally substituted;

or a pharmaceutically accepted salt thereof.

40. The dendrimeric folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36 wherein B is a metal-chelating ligand radical of formula **IIIa** - **IIIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:



wherein

Q is the group $-(C(RR))_{m1}-Y^1(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,
wherein

Y^1 and Y^2 are independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4, provided that the sum of m1 and m2 is greater than zero;

all R and R* groups are independently $-\text{R}^4$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OR}^5$, $-\text{COOR}^5$, $-\text{CON}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{alkyl-COOR}^5$, $-\text{alkyl-C(O)-N}(\text{R}^5)_2$, $-\text{alkyl-N}(\text{R}^5)_2$, $-\text{C(O)OR}^5$, $-\text{C(O)N}(\text{R}^5)_2$, $-\text{aryl-N}(\text{R}^5)_2$, acyl, acyloxy, heterocyclo, hydroxyalkyl, $-\text{SO}_2-\text{R}^5$, $-\text{alkyl-SO}_2-\text{R}^5$, or $-\text{[R}^3\text{]}-$;

wherein $-\text{[R}^3\text{]}-$ is a linking group $-\text{[(A)p]}-$ that couples the metal chelating radical of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule;

$-\text{[(A)p]}-$ comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: $-\text{CH}_2-$, $-\text{CHR}_3-$, $-\text{CR}_4\text{R}_5-$, $-\text{CH=CH}-$, $-\text{CH=CR}_6-$, $>\text{CR}_7-\text{CR}_8<$, $-\text{C=C}-$, $-\text{CR}_9=\text{CR}_{10}-$, $-\text{C}\equiv\text{C}-$, $-\text{cycloalkylidene}-$, $-\text{cycloalkenyl}-$, $-\text{arylidene}-$, $-\text{heterocyclo-}$, carbonyl $-\text{(CO)-}$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{HC=N}-$, $-\text{CR}_{11}=\text{N}-$, $-\text{NR}_{12}-$, $-\text{CS}-$, $-\text{C}-$, $-\text{C}-$, $-\text{N}-$, and

$\text{NR}_{12}-$, $-\text{CS}-$, $-\text{C}-$, $-\text{C}-$, $-\text{N}-$, and

p is an integer from 0 to 24;

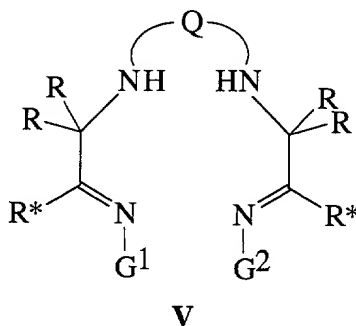
each $-\text{R}^4$ and $-\text{R}_3$ through $-\text{R}_5$ is independently $-\text{H}$, $-\text{alkyl}$, $-\text{alkoxy}$, $-\text{hydroxy}$, $-\text{cycloalkyl}$, $-\text{hydroxyalkyl}$, $-\text{aryl}$, or $-\text{heterocyclo}$, each of which is optionally substituted;

each $-\text{R}^5$ and $-\text{R}_6$ through R_{12} is independently $-\text{H}$, $-\text{alkyl}$, $-\text{aryl}$, $-\text{cycloalkyl}$ or $-\text{hydroxyalkyl}$, each of which is independently substituted;

and all other groups are defined as in claim 35,

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or -R* group on the metal chelating radical -K₁ of formulae **IIIa**, **IIIb**, or **IIIc** is -[R³]-; or a pharmaceutically acceptable salt thereof.

41. The dendrimeric folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim **36**, wherein B is a metal-chelating ligand radical of formula **V** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:



wherein

-Q- is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y¹ and Y² are each independently -CH₂-, -NR-, -O-, -S-, -SO-, -SO₂- or -Se-;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that m1 + m2 + n + n1 is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R* group is independently: -R⁴; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl, -OR⁵, -C(O)-R⁵, -C(O)-N(R⁵)₂, -N(R⁵)₂, -N(R⁵)-COR⁵, -alkyl-C(O)-OR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂-, -alkyl-N(R⁵)-COR⁵, -aryl-C(O)-OR⁵, -aryl-C(O)-N(R⁵)₂, aryl-N(R⁵)₂-, -aryl-N(R⁵)-COR⁵, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

-[R³]- is a linking group -[(A)p]- that links the metal chelating ligand radical of formula **V** to the remainder of the molecule of formulae **IXa**, **IXb**, **IXc**, and **IXd**;

wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-,

-NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-, (-CS-), $-\overset{\text{I}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{C}}}-$, $-\overset{\text{H}}{\underset{\text{I}}{\text{N}}}-$, and

p is an integer from 0 to 24;

each $-R^4$ and $-R_3$ through $-R_5$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R^5$ and $-R_6$ through $-R_{12}$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted; or

two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

each $-G^1$ and $-G^2$ is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of $-G^1$ or $-G^2$ is $-(NR^6)_2$, and each $-R^6$ is independently -

hydrogen, $-alkyl$, $-aryl$, $-acyl$ or $-[R^3]$;
and all other groups are defined as in claim 80,

with the provisos that a carbon atom bearing an $-R$ group is not directly bonded to more than one heteroatom and that at least one $-R$, $-R^*$, or $-R^6$ group on the metal chelating radical $-K_1$ of formula **V** is $-[R^3]$;
or a pharmaceutically acceptable salt thereof.

42. The diagnostic or radiotherapeutic composition of formula **II** of claim 2, wherein K_1 is chelated to a radioactive, paramagnetic or superparamagnetic metal and K_2 is other than $-K_3$.

43. The radiodiagnostic or radiotherapeutic composition of claim 2 wherein both K_1 and K_5 of formula **II** are metal-chelating ligand radicals that are chelated to a radioactive metal.

44. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein either K_1 , or both K_1 and K_5 is chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

45. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either K_1 , or both K_1 and K_5 is chelated to a paramagnetic or superparamagnetic metal.

46. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either K_1 , or both K_1 and K_5 is chelated to gadolinium.

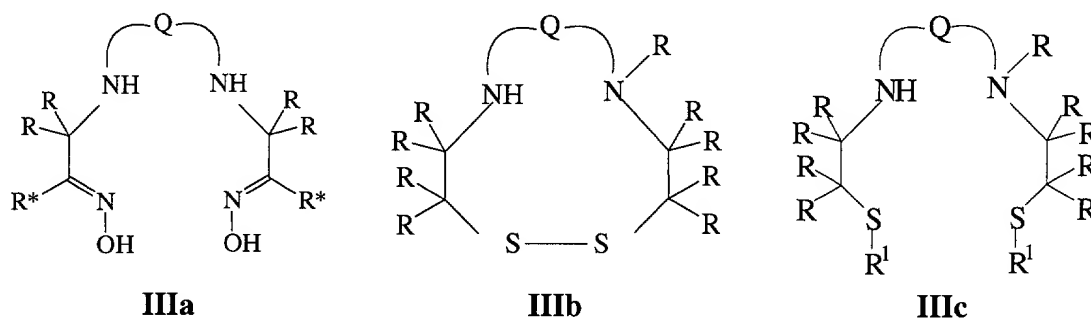
47. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein K_1 is chelated to a paramagnetic or superparamagnetic metal and K_2 is other than $-K_3$.

48. The diagnostic composition of claim 2 for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

49. The diagnostic composition of claim 2, for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein K_1 is chelated to gadolinium.

50. The radiotherapeutic composition of claim 2, for radiotherapy of tissues that overexpress folate binding protein, wherein either K_1 , or both K_1 and K_5 is chelated to a radioisotope selected from the group consisting of $^{153}\text{Samarium}$, $^{156}\text{Holmium}$, $^{165}\text{Dysprosium}$, $^{203}\text{Lead}$, $^{186}\text{Rhenium}$, $^{188}\text{Rhenium}$, $^{88}\text{Yttrium}$, $^{90}\text{Yttrium}$, $^{211}\text{Bismuth}$, $^{212}\text{Bismuth}$, $^{213}\text{Bismuth}$, and $^{214}\text{Bismuth}$.

51. The radiodiagnostic or radiotherapeutic composition of claim 2 wherein either K_1 , or both K_1 and K_5 is a metal-chelating ligand radical of formula IIIa, IIIb, IIIc, that can chelate to a radioactive isotope.



wherein

Q is the group $-(\text{C}(\text{RR}))_{m1}-\text{Y}^1(\text{C}(\text{RR}))_{m2}-(\text{Y}^2-(\text{C}(\text{RR}))_{m3})_n-$,

wherein

Y^1 and Y^2 are independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4, provided that the sum of m1 and m2 is greater than zero;

all R and R* groups are independently $-\text{R}^4$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OR}^5$, $-\text{COOR}^5$, $-\text{CON}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{alkyl-COOR}^5$, $-\text{alkyl-C}(\text{O})-\text{N}(\text{R}^5)_2$, $-\text{alkyl-N}(\text{R}^5)_2$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{C}(\text{O})\text{N}(\text{R}^5)_2$, $-\text{aryl-N}(\text{R}^5)_2$, acyl, acyloxy, heterocyclo, hydroxyalkyl, $-\text{SO}_2-\text{R}^5$, $-\text{alkyl-SO}_2-\text{R}^5$, or $-\text{[R}^3\text{]}-$;

wherein $-\text{[R}^3\text{]}-$ is a linking group $-\text{[(A)p]}-$ that couples the metal chelating radical of formula IIIa, IIIb, or IIIc to the remainder of the molecule;

5
 10
 15
 20

—[(A)p]— comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: —CH₂—, —CHR₃—, —CR₄R₅—, —CH=CH—, —CH=CR₆—, >CR₇—CR₈<, —C=C—, —CR₉=CR₁₀—, —C≡C—, —cycloalkylidene—, —cycloalkenyl—, —arylidene—, —heterocyclo—, carbonyl —(CO)—, —O—, —S—, —NH—, —HC=N—, —CR₁₁=N—, —

NR₁₂—, —CS—, $-\overset{\overset{|}{\text{I}}}{\underset{\underset{|}{\text{I}}}{\text{C}}}-$, $-\overset{\overset{\text{H}}{|}}{\underset{\underset{|}{\text{I}}}{\text{C}}}-$, $-\overset{\overset{\text{H}}{|}}{\underset{\underset{|}{\text{N}}}{\text{N}}}-$, and

p is an integer from 0 to 24;

each —R⁴ and —R₃ through —R₅ is independently —H, —alkyl, —alkoxy, —hydroxy, —cycloalkyl, —hydroxyalkyl, —aryl, or —heterocyclo, each of which is optionally substituted;

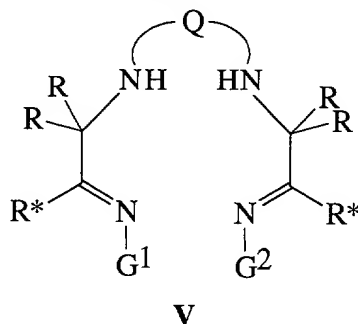
each —R⁵ and —R₆ through —R₁₂ is independently —H, —alkyl, —aryl, —cycloalkyl or —hydroxyalkyl, each of which is independently substituted;

and all other groups are defined as in claim 35,

with the provisos that a carbon atom bearing an —R group is not directly bonded to more than one heteroatom; and that at least one —R or —R* group on the metal chelating radical —K₁ of formulae **IIIa**, **IIIb**, or **IIIc** is —[R³]-;

or a pharmaceutically acceptable salt thereof.

52. A diagnostic or radiotherapeutic composition of claim 2 wherein K₁, or both K₁ and K₅ are metal chelating ligand radical of formula **V** that are chelated to radioactive metals



wherein

—Q— is the group —(C(RR))_{m1}—(Y¹)_n—(C(RR))_{m2}—(Y²—(C(RR))_{m3})_{n1} ;

Y¹ and Y² are each independently —CH₂—, —NR—, —O—, —S—, —SO—, —SO₂— or —Se—;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that m1 + m2 + n + n1 is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each —R and —R* group is independently: —R⁴; —alkoxy; —hydroxy; —halogen, especially fluoro, —haloalkyl, —OR⁵, —C(O)—R⁵, —C(O)—N(R⁵)₂, —N(R⁵)₂, —N(R⁵)—COR⁵, —alkyl—C(O)—OR⁵, —alkyl—C(O)—N(R⁵)₂, —alkyl—N(R⁵)₂—, —alkyl—N(R⁵)—

COR⁵, -aryl-C(O)-OR⁵, -aryl-C(O)-N(R⁵)₂, aryl-N(R⁵)₂-, -aryl-N(R⁵)-COR⁵, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

-[R³]- is a linking group -[(A)p]- that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae VIIa through VIId;

wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<-, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-,

-NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-, (-CS-), $-\overset{\text{H}}{\underset{|}{\text{C}}}-$, $-\overset{\text{H}}{\underset{|}{\text{C}}}-$, $-\overset{\text{H}}{\underset{|}{\text{N}}}-$, and

p is an integer from 0 to 24;

each -R⁴ and -R₃ through -R₅ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R⁵ and R₆ through R₁₂ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

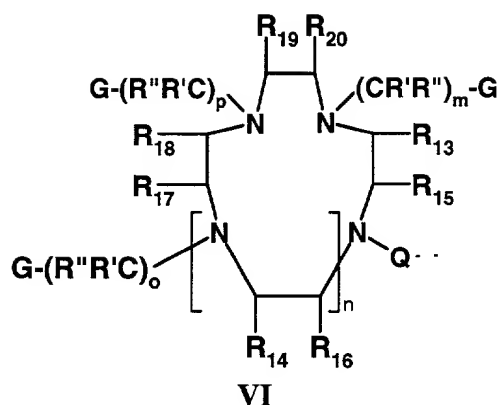
two R groups, or an R group and an R* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R* groups above;

each -G¹ and -G² is independently -OH or -(NR⁶)₂; with the proviso that at least one of -G¹ or -G² is -(NR⁶)₂, and each -R⁶ is independently -hydrogen, -alkyl, -aryl, -acyl or -[R³]-;

with the proviso that at least one -R, -R*, or -R⁶ group is -[R³]-;

or a pharmaceutically acceptable salt thereof.

53. The diagnostic composition of claim 46, wherein either K₁, or both K₁ and K₅ is a metal-chelating ligand radical of formula VI, that is chelated to a paramagnetic or superparamagnetic metal



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is $-\text{C}(\text{R}')(\text{R}'')_{s1}-\text{C}(\text{t})(\text{R}_{21})_{s2}-\text{C}(\text{R}_{22})(\text{R}_{23})_{s3}-\text{X3}-\text{Y}-\text{X4}-$;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

Y is a single bond, $-\text{C}(\text{R}_{25})(\text{R}_{26})-$, or Y1 wherein,

Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R27, $-\text{C}(\text{O})\text{OR}_{28}$, $-\text{P}(\text{O})(\text{OR}_{29})\text{OH}$, $-\text{P}(\text{O})(\text{OR}_{30})\text{OR}_{31}$,

$-\text{P}(\text{O})(\text{OR}_{32})\text{R}_{33}$, $-\text{P}(\text{O})(\text{OH})\text{R}_{34}$, $-\text{C}(\text{O})\text{N}(\text{R}_{35})(\text{R}_{36})$, or $\text{C}(\text{O})\text{NH}(\text{R}_{37})$;

each G is independently $-\text{C}(\text{O})\text{OR}'''$, $-\text{P}(\text{O})(\text{OR}''')\text{OH}$, $-\text{P}(\text{O})(\text{OR}''')_2$,

$-\text{P}(\text{O})(\text{OR}''')\text{R}''$, $-\text{P}(\text{O})(\text{OH})\text{R}''$, $\text{C}(\text{O})\text{N}(\text{R}''')_2$, or $\text{C}(\text{O})\text{NH}(\text{R}''')$;

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R13 through -R23, and -R25 through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;

each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with R18, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R13,

together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen; or a pharmaceutically acceptable salt thereof.

5 54. A composition for radiographic imaging or radiotherapy in a kit form comprising
 a) a ligand of formula **II** in claim 2;
 b) a pharmaceutically acceptable reducing agent; and
 c) an optional buffering agent;
 in a lyophilized form.

10 55. A method for diagnostic imaging comprising the steps of:
 a) administering to a host the composition of claim 2 wherein K₁ is chelated to a radioactive, paramagnetic or superparamagnetic metal and K₂ is other than - K₃; and
 b) obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic
 15 Resonance imaging techniques.

56. A method for diagnostic imaging comprising the steps of:
 a) administering to a host a composition of claim 2 wherein both K₁ and K₅ are
 chelated to a radioactive, paramagnetic or superparamagnetic metal; and
 20 b) obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic
 Resonance imaging techniques.

57. A method for radiotherapy comprising the steps of: administering to a host in need
 thereof the composition of claim 2 wherein K₁ or both K₁ and K₅ are chelated to an alpha
 25 or beta emitting radioisotope.

58. A method for radiotherapy comprising the steps of: administering to a host in need
 thereof the composition of claim 2 wherein K₁ is chelated to an alpha- or beta- emitting
 radioisotope and K₂ is other than - K₃.

30 59. The diagnostic or radiotherapeutic composition of claim 1 wherein the folate
 receptor binding moiety is conjugated to the remainder of the molecule through the alpha
 carboxylate of its glutamate residue.

35 60. A composition for radiographic imaging or radiotherapy in a kit form comprising
 a) a folate receptor binding ligand of formula **II** in claim 2;
 b) a pharmaceutically acceptable reducing agent; and
 c) an optional buffering agent;
 in a lyophilized form.

40 61. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of
 claim 2, comprising coinjection of :

a) a folate-receptor binding ligand comprised of one or more folate-receptor binding
 residues conjugated to one or more macrocyclic or non-macrocyclic metal-
 45 chelating ligands which are chelated to a radioactive or non-radioactive metal

capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and

- b) an unmetallated derivative of said folate-receptor binding ligand, administered at a dose level sufficient to affect the resulting biodistribution of the composition.

5

62. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of claim **2** chelated to gadolinium, and after localization in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue is damaged.

10

63. The diagnostic or radiodiagnostic method of claim **55** wherein said image is of tumors or tissues that overexpress folate binding protein.

15

64. The diagnostic or radiodiagnostic method of claim **55** wherein said image is of the kidneys of said host.

65. The diagnostic or radiodiagnostic method of claim **55** wherein said image is of the hepatobiliary system of said host.

20

66. The diagnostic or radiodiagnostic method of claim **56** wherein said image is of tumors or tissues that overexpress folate binding protein.

67. The diagnostic or radiodiagnostic method of claim **56** wherein said image is of the kidneys of said host.

25

68. The diagnostic or radiodiagnostic method of claim **56** wherein said image is of the hepatobiliary or gastrointestinal system of said host.

30

69. The diagnostic composition of formula **VIIa, VIIb, VIIc, or VIId** of claim **29**, wherein W_1 contains metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

35

70. The diagnostic composition of formula **VIIa, VIIb, VIIc, or VIId** of claim **29**, wherein both W_1 and W_2 contains metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

40

71. The radiodiagnostic or radiotherapeutic composition of formula **VIIa – VIId** of claim **29** wherein W_1 contains metal-chelating ligands that are chelated to a radioactive metal.

72. The radiodiagnostic or radiotherapeutic composition of formula **VIIa – VIId** of claim **29** wherein both W_1 and W_2 contain metal-chelating ligands that are chelated to a radioactive metal.

45

73. The diagnostic composition of formula **VIIa – VIId** of claim **29** for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

74. The diagnostic composition of formula **VIIa – VIId** of claim **29** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands chelated to a paramagnetic or superparamagnetic metal.

75. The diagnostic composition of claim **74** wherein either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands that are chelated to gadolinium.

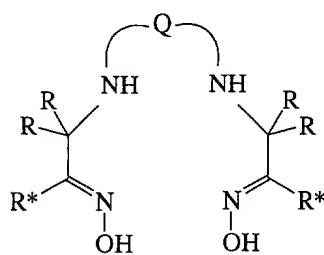
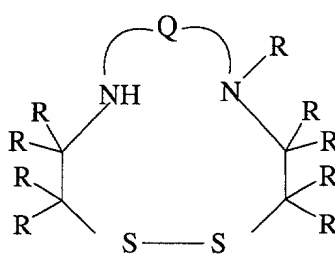
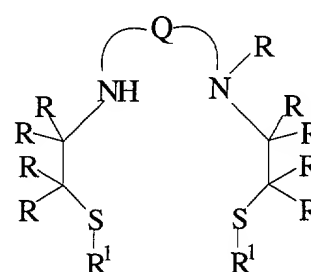
76. The diagnostic composition of claim **74** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein W_1 contains metal chelating ligands that are chelated to paramagnetic or superparamagnetic metals.

77. The diagnostic composition of claim **74** for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

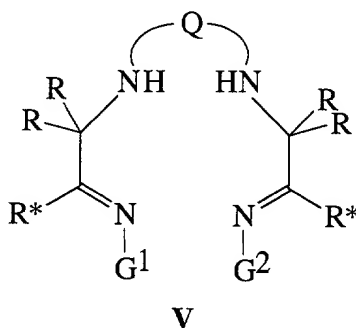
78. The diagnostic composition of claim **74** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein K_1 is chelated to gadolinium.

79. The radiotherapeutic composition of claim **72** for radiotherapy of tissues that overexpress folate binding protein, wherein either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands that are chelated to a radioisotope selected from the group consisting of $^{153}\text{Samarium}$, $^{156}\text{Holmium}$, $^{165}\text{Dysprosium}$, $^{203}\text{Lead}$, $^{186}\text{Rhenium}$, $^{188}\text{Rhenium}$, $^{88}\text{Yttrium}$, $^{90}\text{Yttrium}$, $^{211}\text{Bismuth}$, $^{212}\text{Bismuth}$, $^{213}\text{Bismuth}$, and $^{214}\text{Bismuth}$.

80. The radiodiagnostic or radiotherapeutic composition of claim **72** wherein either W_1 , W_2 or both W_1 and W_2 contain a metal-chelating ligand radical of formula **IIIa**, **IIIb**, or **IIIc**, that can chelate to a radioactive isotope,

**IIIa****IIIb****IIIc**

81. A diagnostic or radiotherapeutic composition of claim 29 wherein W_1 , W_2 or both W_1 and W_2 contain metal chelating ligands of formula V that are chelated to a radioactive metal,



wherein

Q is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2)-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are independently 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and R^* group is independently: $-H$, $-R^4$; $-alkoxy$; $-hydroxy$; $-halogen$, especially fluoro, $-haloalkyl$, $-OR^5$, $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$, $-alkyl-C(O)-OR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-alkyl-N(R^5)-COR^5$, $-aryl-C(O)-OR^5$, $-aryl-C(O)-N(R^5)_2$, $aryl-N(R^5)_2$, $-aryl-N(R^5)-COR^5$, $-nitrile$, $-acyl$, $-acyloxy$, $-heterocyclo$, $-hydroxyalkyl$, $-alkoxyalkyl$, $-hydroxyaryl$, $-arylalkyl$, $-SO_2-R^5$, $-alkyl-SO_2-R^5$, or $-[R^3]-$;

wherein

each $-[R^3]-$ is, in its entirety, the linking group $-[(A)p^*]-$ that serves to couple the metal chelating ligand radical $-K_5$ to $-X-$;

each $-R^4$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R^5$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted;

or

two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

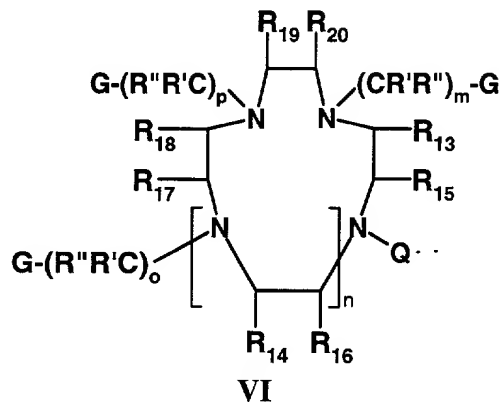
each $-G^1$ and $-G^2$ is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of $-G^1$ or $-G^2$ is $-(NR^6)_2$, where each $-R^6$ is independently $-hydrogen$, $-alkyl$, $-aryl$, $-acyl$ or $-[R^3]-$; and

A is a linking group; and p is 0 or a positive integer;

with the proviso that at one to three $-R$, $-R^*$, or $-R^6$ groups is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.

82. The diagnostic composition of claim 29, wherein either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands of formula VI that are chelated to a paramagnetic or superparamagnetic metal,



wherein

n is 0 or 1;

each m , o , and p is independently 1 or 2;

$-Q-$ is $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$;

wherein

$s1$, $s2$, $s3$, and $s4$ are independently 0 to 2;

$X3$, $X4$, $X5$, and $X6$ are independently a single bond, $-O-$, $-S-$, or $-N(R_{24})-$;

Y is a single bond, $-C(R_{25})(R_{26})-$, or $Y1$

wherein $Y1$ is $-C(=X5)-X6-W-$,

wherein W is a single bond, $-alkylidene-$, $-cycloalkylidene-$, $-arylidene-$, $-alkenylidene-$, or $-alkynylidene-$, whose carbon atoms may or may not be substituted;

t is $-H$, $-R_{27}$, $-C(O)OR_{28}$, $-P(O)(OR_{29})OH$, $-$

$P(O)(OR_{30})OR_{31}$, $-P(O)(OR_{32})R_{33}$, $-P(O)(OH)R_{34}$, $-C(O)N(R_{35})(R_{36})$, or $C(O)NH(R_{37})$;

each G is independently $-C(O)OR'''$, $-P(O)(OR''')OH$, $-P(O)(OR''')_2$, $-P(O)(OR'')R'''$, $-P(O)(OH)R''$

$C(O)N(R''')_2$, or $C(O)NH(R''')$;

each $-R'$ and $-R''$ is independently a single bond, $-H$, $-alkyl$, $-alkoxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted,

each $-R'''$ is independently a $-H$, $-alkyl$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted,

each $-R_{13}$ through $-R_{23}$, and R_{25} through $-R_{27}$ is independently $-H$, $-alkyl$, $-alkoxy$, $-halogen$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;
 or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with
 5 the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic
 10 cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;
 or a pharmaceutically acceptable salt thereof.

15 83. A composition for radiographic imaging or radiotherapy in a kit form comprising
 a) a ligand of formula **VIIa-VIIId** in claim **29**;
 b) a pharmaceutically acceptable reducing agent; and
 c) an optional buffering agent;
 in a lyophilized form.

20 84. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim **29** wherein W₁ contains a metal chelate that is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

25 85. A method for diagnostic imaging comprising the steps of: administering to a host a composition of claim **29** wherein both W₁ and W₂ contains a metal chelate that is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

30 86. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim **29** wherein W₁ or both W₁ and W₂ contain macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

35 87. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim **29** wherein W₁ contains macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

40 88. The diagnostic or radiotherapeutic composition of claim **29** wherein the folate receptor binding moiety is conjugated to the remainder of the molecule through the alpha carboxylate of its glutamate residue.

89. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of claim **29**, comprising coinjection of :

- a) a folate-receptor binding ligand comprised of one or more folate-receptor binding residues conjugated to one or more macrocyclic or non-macrocyclic metal-chelating ligands which are chelated to a radioactive or non-radioactive metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and
- b) an unmetallated derivative of said folate-receptor binding ligand, administered at a dose level sufficient to affect the resulting biodistribution of the composition.

90. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of formula **VIIa-VIIId** of claim **29** wherein the metal chelating ligands in W_1 , W_2 or W_1 and W_2 are chelated to gadolinium, and after localization of said compound in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue is damaged.

91. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of tumors or tissues that overexpress folate binding protein.

92. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of the kidneys of said host.

93. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of the hepatobiliary system of said host.

94. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of tumors or tissues that overexpress folate binding protein.

95. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of the kidneys of said host.

96. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of the hepatobiliary system of said host.

97. A method for diagnostic imaging comprising the steps of: administering to a host the diagnostic composition of claim **29** comprising dendrimeric conjugates of formulae **VIIa, VIIb, VIIc, or VIId**, wherein W_1 contains metal chelating ligands that are chelated to a radioactive gamma-emitting metal, and obtaining a radiodiagnostic image of said host.

98. The diagnostic composition of formulae **IXa, IXb, IXc, or IXd** of claim **36** containing metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

99. The diagnostic composition of formula **IXa, IXb, IXc, or IXd** of claim **98** wherein the folate receptor binding residues are chelated to the remainder of the molecule only

through the alpha carboxylate residue.

100. The diagnostic composition of formula **IXa**, **IXb**, **IXc**, or **IXd** of claim **36** for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein said compounds contain macrocyclic metal-chelating ligands chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

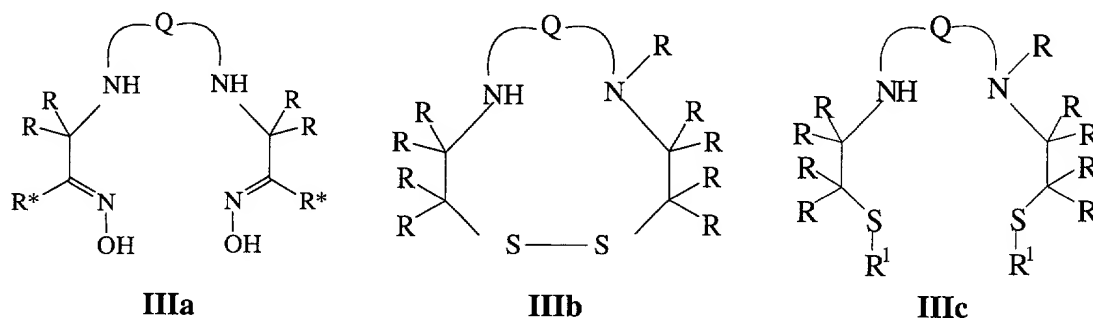
101. The diagnostic composition of formula **IXa**, **IXb**, **IXc**, or **IXd** of claim **36** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein the folate-receptor binding residue is conjugated to the remainder of the molecule via its alpha carboxylate moiety, and the compound contains macrocyclic metal-chelating ligands chelated to a paramagnetic or superparamagnetic metal.

102. The diagnostic composition of claim **101** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging wherein, either W_1 , W_2 or both W_1 and W_2 contain metal-chelating ligands that are chelated to gadolinium.

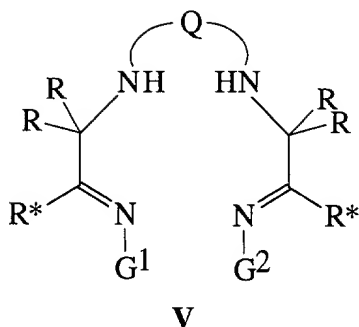
103. The diagnostic composition of claim **101** for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

104. The radiotherapeutic composition of claim **36** for radiotherapy of tissues that overexpress folate binding protein, containing metal-chelating ligands that are chelated to a radioisotope selected from the group consisting of $^{153}\text{Samarium}$, $^{156}\text{Holmium}$, $^{165}\text{Dysprosium}$, $^{203}\text{Lead}$, $^{186}\text{Rhenium}$, $^{188}\text{Rhenium}$, $^{88}\text{Yttrium}$, $^{90}\text{Yttrium}$, $^{211}\text{Bismuth}$, $^{212}\text{Bismuth}$, $^{213}\text{Bismuth}$, and $^{214}\text{Bismuth}$.

105. The radiodiagnostic or radiotherapeutic composition of claim **36**, wherein the metal-chelating ligand is a radical of formula **IIIa**, **IIIb**, or **IIIc**.



106. The radiodiagnostic or radiotherapeutic composition of claim **36** wherein the metal-chelating ligand is a radical of formula **V** that is chelated to a radioactive metal,



wherein

-Q- is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R* group is independently: $-R^4$; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl, $-OR^5$, $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$, -alkyl- $C(O)-OR^5$, -alkyl- $C(O)-N(R^5)_2$, -alkyl- $N(R^5)_2$, -alkyl- $N(R^5)-COR^5$, -aryl- $C(O)-OR^5$, -aryl- $C(O)-N(R^5)_2$, aryl- $N(R^5)_2$, -aryl- $N(R^5)-COR^5$, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, $-SO_2-R^5$, -alkyl- $-SO_2-R^5$, or $-[R^3]-$;

wherein

$-[R^3]-$ is a linking group $-[(A)p]-$ that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae VIIa through VIId;

wherein $-[(A)p]-$ comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: $-CH_2-$, $-CHR_3-$, $-CR_4R_5-$, $-CH=CH-$, $-CH=CR_6-$, $>CR_7-CR_8<$, $-C=C-$, $-CR_9=CR_{10}-$, $-C\equiv C-$, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ($-CO-$), $-O-$, $-S-$,

$-NH-$, $-HC=N-$, $-CR_{11}=N-$, $-NR_{12}-$, $(-CS-)$, $-\overset{|}{C}-$, $-\overset{H}{\underset{|}{C}}-$, $-\overset{H}{\underset{|}{N}}-$, and

p is an integer from 0 to 24;

each $-R^4$ and $-R_3$ through $-R_5$ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each $-R^5$ and $-R_6$ through $-R_{12}$ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

two R groups, or an R group and an R* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated,

spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R* groups above;

each -G¹ and -G² is independently -OH or -(NR⁶)₂; with the proviso that at

5 least one of -G¹ or -G² is -(NR⁶)₂, and each -R⁶ is independently - hydrogen, -alkyl, -aryl, -acyl or -[R³]-;

with the proviso that at least one -R, -R*, or -R⁶ group is -[R³]-;

or a pharmaceutically acceptable salt thereof.

10 107. The diagnostic composition of claim **36** wherein the metal-chelating ligand is a radical of formula **VI** that is chelated to a paramagnetic or superparamagnetic metal.

108. A composition for radiographic imaging or radiotherapy in a kit form comprising

a) a ligand of formula **IXa - IXd** in claim **36**;

15 b) a pharmaceutically acceptable reducing agent; and

c) an optional buffering agent;

in a lyophilized form.

20 109. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim **108** wherein said ligand of formula **IXa - IXd** is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

25 110. A method for radiotherapy comprising the steps of: administering to a host the composition of formula **IXa - IXd** of claim **36** containing macrocyclic metal chelating ligands that are chelated to an alpha or beta emitting radioisotope, in sufficient amount to bring about a beneficial effect.

30 111. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim **36** wherein W₁ contains macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

35 112. The use of diagnostic or radiotherapeutic composition of claim **36** for magnetic resonance imaging, wherein the folate receptor binding moieties in said compound are conjugated to the remainder of the molecule through the alpha carboxylate of its glutamate residue.

40 113. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of claim **36** comprising: coinjection of :

a) a folate-receptor binding ligand comprised of one or more folate-receptor binding residues conjugated to one or more macrocyclic or non-macrocyclic metal-chelating ligands which are chelated to a radioactive or non-radioactive metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and

45 b) an unmetallated derivative of said folate-receptor binding ligand,

administered at a dose level sufficient to affect the resulting biodistribution of the composition.

114. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of formulae **IXa-IXd** of claim **36** wherein the metal chelating ligands are chelated to gadolinium, and after localization of said compound in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue is damaged.

115. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of tumors or tissues that overexpress folate binding protein.

116. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of the kidneys of said host.

117. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of the hepatobiliary system of said host.

118. The composition of claim **1** for chemotherapy comprising: a derivative of folic acid coupled to a cancer therapy drug through the alpha carboxylate of folic acid, or coupled through both the alpha and gamma carboxylates of folic acid, in a pharmaceutically acceptable carrier.

119. A composition for therapy or radiotherapy of tissues or organs that overexpress folate-binding protein comprising a folate-receptor binding derivative of folic acid comprising one or more folic acid derivatives, at least one of which is conjugated through its alpha carboxylate via an optional linking group to a chemotherapeutic drug, in a pharmaceutically acceptable carrier.

120. A composition of claim **1** for chemotherapy comprising:
a) a metal chelating ligand;
b) a radioactive metal chelated by said ligand;
c) a chemotherapy drug coupled to said ligand said complex coupled to
d) a derivative of folic acid through its alpha carboxylate or through both the alpha and gamma carboxylate of folic acid, in
e) a pharmaceutically acceptable carrier.

121. A composition of claim **1** for radiographic imaging or radiotherapy in a kit form comprising

- a) a folate receptor-binding analog of folate coupled through either the alpha carboxylate of folic acid or through both the alpha and gamma carboxylates of folic acid to;
- b) a metal chelating ligand for complexation with a radioisotope;
- c) a pharmaceutically acceptable reducing agent; and
- d) a buffering agent;

in a lyophilized form.

122. The diagnostic composition of claim **18** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein K₅ is chelated to gadolinium.

123. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim **18** wherein said ligand is chelated to gadolinium; and obtaining a diagnostic image using Magnetic Resonance imaging techniques.

124. An intermediates useful for the preparation of the compounds of claim **1** selected from the group consisting of:

Methyl 3-azido-2-hydroxypropionate;

Methyl 3-azido-2-trifluoromethanesulfonyloxypropionate;

Tris-t-butyl N-12-(3-azido-2-methoxycarbonyl-1-ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate;

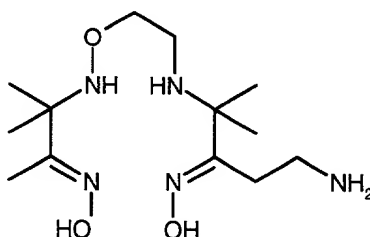
Tris-t-butyl N-12-(3-amino-2-methoxycarbonyl-1-ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate;

3-Amino-[1,5-bis(benzyloxycarbonyl)-3-[2-(benzyloxycarbonyl)ethyl]pentane;

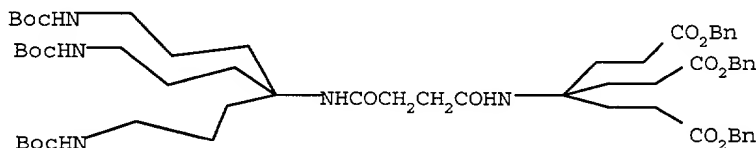
and

N-[1,5-Bis[benzyloxycarbonyl]-3-[2-(benzyloxycarbonyl)ethyl]-3-pentyl]-butanedioic monoamide.

125. The intermediate 12-Amino-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecane-dione dioxime, useful for the preparation of compounds of claim **1** having the structure:



126. The intermediate N-[1,5-Bis(benzyloxycarbonyl)-3-[2-(benzyloxycarbonyl)-ethyl]-3-pentyl]-N'-[1,7-bis-(t-butoxycarbonyl)amino-[4-(3-(t-butyloxycarbonyl)propyl)-4-heptyl]butanedioic diamide, useful for the preparation of compounds of claim **35** having the structure:



127. The intermediate Tris-t-butyl N-12-(3-amino-2-methoxycarbonyl-1-ethyl)-1,4,7,10-

tetracyclododecane-1,4,7-tricarboxylate useful for the preparation of compounds of claim 28, having the structure:

